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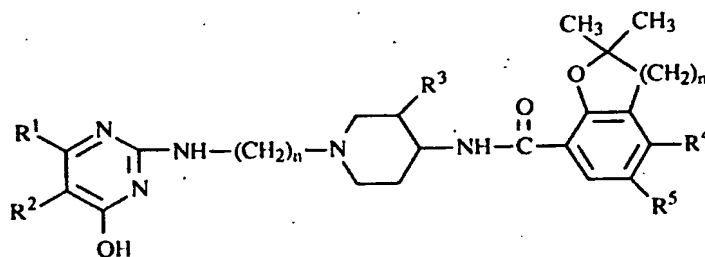
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(54) Title: USE OF DIMETHYLBENZOFURANS AND DIMETHYLBENZOPYRANS AS 5-HT₃ ANTAGONISTS

(57) Abstract

Method of treating 5-HT₃-mediated disorders, which comprises systemic administration of an effective amount of a compound of formula (I), the pharmaceutically acceptable acid addition salt forms and the stereochemically isomeric forms thereof, wherein R¹ and R² represent hydrogen, or R¹ and R² taken together form a bivalent radical of formula (a): -CH = CH-CH = CH-, (b): -CH = C(Cl)-CH = CH- or (c): -CH = CH-C(Cl) = CH-; n represents 2, 3 or 4; R³ represents hydrogen or methoxy; m represents 1 or 2; R⁴ represents hydrogen, amino or C₁₋₃-alkylcarbonylamino; and R⁵ represents hydrogen or halo; novel compounds; compositions; processes for preparing novel compounds and intermediates.



(I)

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Use of dimethylbenzofurans and dimethylbenzopyrans as 5-HT₃ antagonists

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Background of the invention

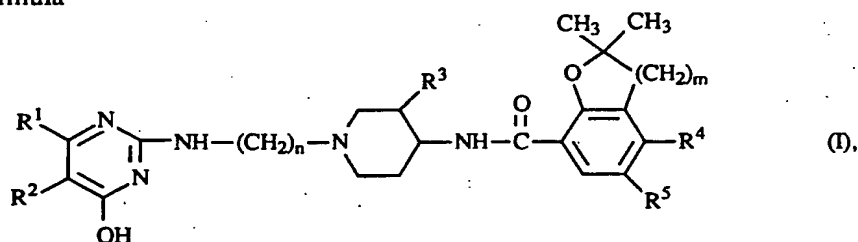
EP-0,389,037, published on September 26, 1990 discloses N-(3-hydroxy-4-piperidiny)(dihydrobenzofuran, dihydro-2H-benzopyran or dihydrobenzodioxin) carboxamide derivatives and EP-0,445,862, published on September 11, 1991 discloses N-(4-piperidiny)(dihydrobenzofuran or dihydrobenzo-2H-benzopyran)carboxamide derivatives. Both applications disclose gastrointestinal motility stimulating properties for said compounds. The dimethyl-dihydrobenzofuran and dimethyl-dihydro-2H-benzopyran derivatives of the present invention show 5-HT₃-antagonism.

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Description of the invention

The present invention is concerned with a method of treating warm-blooded animals suffering from 5-HT₃ mediated disorders such as anxiety, psychosis, depression, schizophrenia, cognitive disorders, drug abuse, migraine, emesis, irritable bowel syndrome and related disorders, which comprises the systemic administration to said warm-blooded animals of an effective 5-HT₃ antagonistic amount of a compound of formula

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a pharmaceutically acceptable acid addition salt form or a stereochemically isomeric form thereof, wherein

R¹ and R² represent hydrogen, or

R¹ and R² taken together form a bivalent radical of formula

30

-CH=CH-CH=CH- (a),

-CH=C(Cl)-CH=CH- (b) or

-CH=CH-C(Cl)=CH- (c);

n represents 2, 3 or 4;

R³ represents hydrogen or methoxy;

m represents 1 or 2;

R⁴ represents hydrogen, amino or C₁₋₃alkylcarbonylamino; and

R⁵ represents hydrogen or halo.

5

The present invention is also concerned with the use of the compounds of formula (I), the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof for the manufacture of a medicament for treating 5-HT₃ mediated disorders such as anxiety, psychosis, depression, schizophrenia, cognitive disorders, drug abuse, migraine, emesis, irritable bowel syndrome and related disorders.

10

In the foregoing definitions and hereinafter the term halo defines fluoro, chloro, bromo and iodo, preferably chloro; C₁₋₄alkyl defines straight and branch chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl, preferably methyl. C₁₋₆alkyl defines C₁₋₄alkyl and the higher homologues thereof such as, for example, pentyl and hexyl. C₁₋₃alkylcarbonyl defines straight and branch chained acyl radicals such as methylcarbonyl, ethylcarbonyl, propylcarbonyl, preferably methylcarbonyl.

20

The term pharmaceutically acceptable acid addition salt as used hereinbefore defines the non-toxic, therapeutically active acid addition salt forms which the compounds of formula (I) may form. The compounds of formula (I), having basic properties, may be converted into the corresponding therapeutically active, non-toxic acid addition salt forms by treating the free base form with a suitable amount of an appropriate acid following conventional procedures. Examples of appropriate acids are inorganic acids, for example, hydrohalic acid, e.g. hydrochloric, hydrobromic and the like acids, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, cyclohexane-sulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. The term pharmaceutically acceptable addition salts also comprises the solvates which the compounds of formula (I) may form such as alcoholates and in particular hydrates.

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The compounds of formula (I) may also exist in their tautomeric form. Said form although not explicitly indicated hereinabove is intended to be included within the scope of the present invention.

The term stereochemically isomeric forms as used hereinbefore defines the different isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers, and/or enantiomers of the basic molecular structure. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Hereinafter the term 'enantiomerically pure' concerns compounds having an enantiomeric excess of at least 94% (i.e. minimum 97% of one enantiomer and maximum 3% of the other enantiomer) up to an enantiomeric excess of 100% (i.e. 100% of one enantiomer and none of the other), in particular compounds having an enantiomeric excess of 96% up to 100%, more in particular having an enantiomeric excess of 98% up to 100%. The term "enantiomerically enriched" concerns compounds having an enantiomeric excess ranging from more than 0 % up to about 94%. The terms "diastereomerically enriched" and "diastereomerically pure" as used hereinafter should be understood in a similar way, but then having regard to the diastereomeric excess of the mixture in question.

Interesting compounds for use as 5-HT₃ antagonists are those compounds of formula (I) wherein R⁵ is halo, preferably chloro.

Also interesting compounds for use as 5-HT₃ antagonists are those compounds of formula (I) wherein R⁴ represents hydrogen or amino.

More interesting compounds for use as 5-HT₃ antagonists are those compounds of formula (I) wherein

R¹ and R² represent hydrogen;

n represents 2 or 3;

R³ represents methoxy and has the cis-configuration;

m represents 1;

R⁴ represents amino; and

R⁵ represents halo.

Particularly interesting compounds for use as 5-HT₃ antagonists are those interesting compounds of formula (I), wherein R³ is methoxy having the cis-configuration, that are laevo-rotatory.

Preferred compounds are (-)-cis-4-amino-5-chloro-2,3-dihydro-N-[1-[3-[(3,4-dihydro-4-oxo-2-pyrimidinyl)amino]propyl]-3-methoxy-4-piperidinyl]-2,2-dimethyl-7-benzofurancarboxamide and (-)-cis-4-amino-5-chloro-N-[1-[2-[(3,4-dihydro-4-oxo-2-pyrimidinyl)amino]ethyl]-2,3-dihydro-3-methoxy-4-piperidinyl]-2,2-dimethyl-7-benzofurancarboxamide, and the pharmaceutically acceptable acid addition salts thereof.

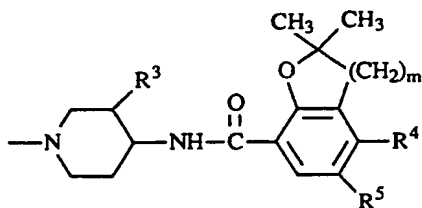
The compounds of formula (I), wherein R^3 is methoxy and has the cis-configuration are represented by formula (I-a). Hereinafter the intermediates wherein R^3 is methoxy and where possible has the cis-configuration will be designated by appending the suffix -a to their numerical reference.

An additional feature of the present invention comprises the fact that the laevo-rotatory enantiomers of the compounds of formula (I) wherein R^3 represents methoxy and has the cis-configuration, i.e. the laevorotatory enantiomers of the compounds of formula (I-a), are deemed novel.

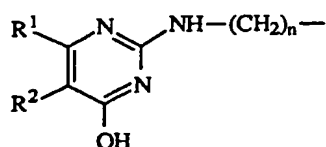
The compounds of formula (I) can generally be prepared following art-known procedures such as described in EP-0,389,037 and alternative processes known in the art. Some intermediates of formula (II), (III), (IV), (V), (VI), (VII), (IX), (X) and (XIII) are described in EP-0,389,037, EP-0,445,862 and EP-0,076,350. Some methods for preparing compounds of formula (I), especially compounds of formula (I-a), and novel intermediates will be described hereinunder.

In the following preparations, the reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, distillation, crystallization, trituration and chromatography.

In order to simplify the structural representations of the compounds of formula (I) and certain starting materials and intermediates thereof, the radical

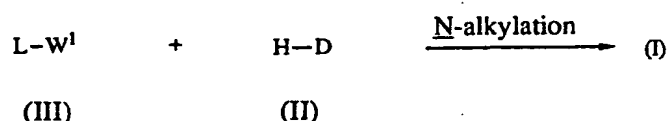


will hereafter be represented by the symbol D and the radical



will hereafter be represented by L.

The compounds of formula (I) may be prepared by N-alkylating a piperidine of formula (II) with an intermediate of formula (III).



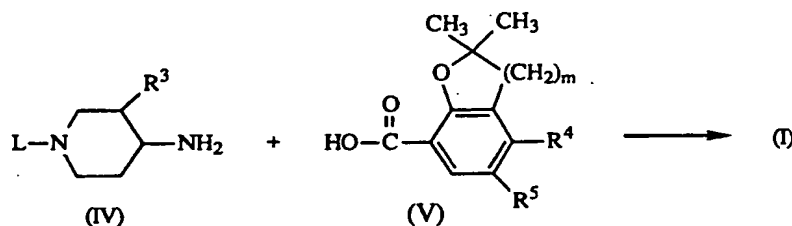
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W¹ as described in the reaction of (III) with (II) and in the following reaction schemes is an appropriate leaving group such as, for example, halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methanesulfonyloxy, 4-methylbenzenesulfonyloxy and the like leaving groups. The N-alkylation reaction of (II) with (III) is conveniently conducted following art-known alkylation procedures.

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The compounds of formula (I) may also be prepared by the N-acylation of an amine of formula (IV) with a carboxylic acid of formula (V) or a functional derivative thereof, such as an acylhalide, a symmetrical or mixed anhydride or an ester, preferably an activated ester, following art-known procedures.

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It may be expedient to protect amino or hydroxy groups during the course of the reaction to avoid undesired side reactions. Suitable protecting groups comprise readily removable groups such as C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, phenylmethyl, tertiary butyl and the like protective groups.

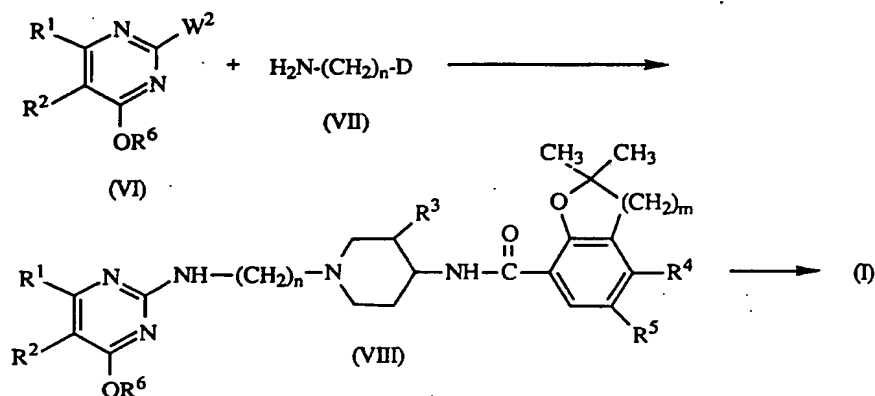
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The compounds of formula (I) may also be prepared by N-alkylating an intermediate of formula (VII) with an alkylating reagent of formula (VI), wherein R⁶ is hydrogen or C₁₋₆alkyl and W² is an appropriate leaving group such as, for example, halo, e.g. chloro, bromo or iodo; a sulfonyloxy group, e.g. methanesulfonyloxy, 4-methylbenzenesulfonyloxy; C₁₋₆alkyloxy, e.g. methoxy, ethoxy; C₁₋₆alkylthio, e.g. methyl-

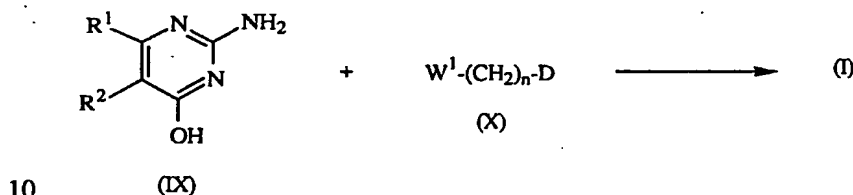
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thio, ethylthio. When R^6 is C_{1-6} alkyl an intermediate of formula (VIII) is formed, which may subsequently be transformed into the final compounds by cleaving the protective etherfunction. Said cleavage may be carried out by treating the intermediate of formula (VIII) with an acid, such as, for example, a hydrohalic acid, e.g. hydrochloric acid.

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The compounds of formula (I) can alternatively be prepared by N -alkylating an 2-amino-pyridine of formula (IX) with an intermediate of formula (X).



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The alkylation reactions of (VI) with (VII) and (IX) with (X) may be carried out according to art-known procedures, e.g. by stirring and optionally heating the reactants without solvent or in admixture with an inert organic solvent such as, for example an alcohol, e.g. 2-propanol, butanol, a dipolar aprotic solvent, e.g. acetonitrile optionally in the presence of an appropriate base, e.g. potassium carbonate.

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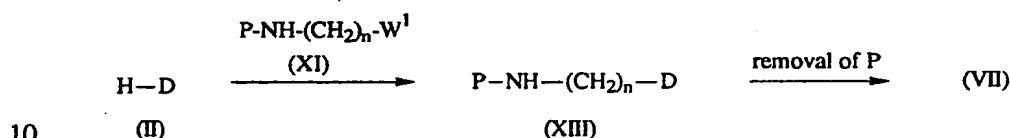
The compounds of formula (I) may also be converted into each other following art-known group-transformation reactions.

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Aminogroups may be transformed in C_{1-3} alkylcarbonylamino by art-known N -acylation reactions and conversely C_{1-3} alkylcarbonylamino groups may be transformed in amino groups using art-known hydrolysis reactions.

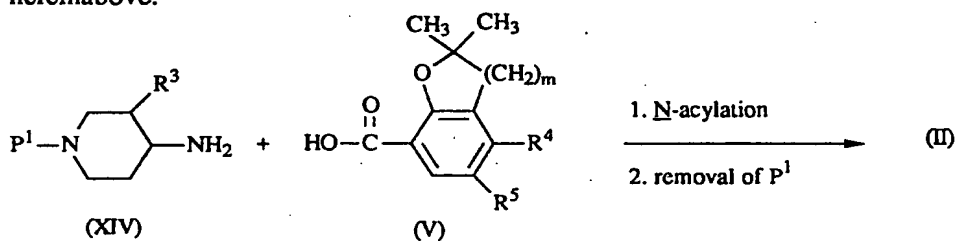
Compounds of formula (I), wherein R^5 is hydrogen may be transformed in the corresponding compounds wherein R^5 is halogen, using art-known halogenation techniques.

- 5 The intermediates of formula (VII) may be prepared by N-alkylating an intermediate of formula (II) with a reagent of formula (XI) and subsequently removing the protective group P in the thus obtained intermediate (XIII) following art-known reaction procedures.



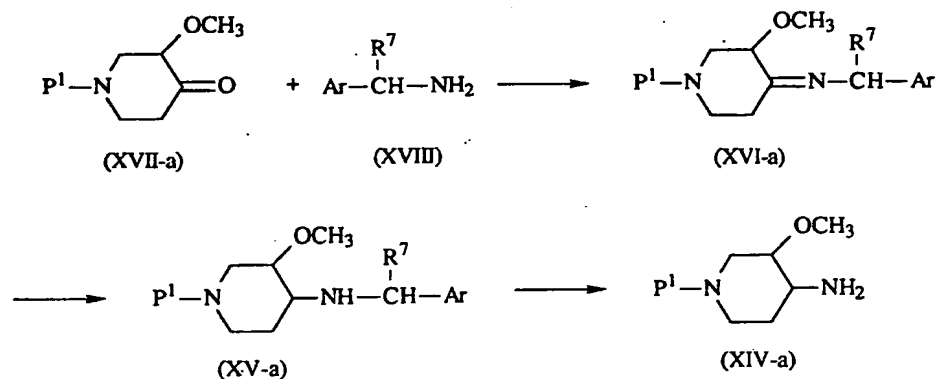
- In (XI), (XIII) and the other intermediates containing the group P in the following schemes, P represents a suitable protective group which is readily removable by, for example, hydrogenolysis or hydrolysis. Preferred protective groups are, for example,
- 15 C_{1-4} alkylcarbonyl, e.g. methylcarbonyl, ethylcarbonyl; C_{1-4} alkoxycarbonyl, e.g. ethoxycarbonyl, 1,1'-dimethylethoxycarbonyl; trihalomethylcarbonyl, e.g. trifluoromethylcarbonyl; diphenylmethyl; triphenylmethyl or arylmethyl, wherein aryl is phenyl optionally substituted with up to two substituents selected from C_{1-4} alkyloxy or halo.

- 20 The intermediates of formula (II) may be derived from an appropriately substituted piperidine of formula (XIV) with an intermediate acid of formula (V) or a functional derivative thereof, following art-known amide forming procedures, and subsequently removing the protective group P^1 , following art-known procedures. P^1 represents a readily removable protective group and has the same meaning as the group P
- 25 hereinabove.



- The intermediates of formula (XIV), wherein R^3 is methoxy and has the cis-configuration, i.e. the 3-methoxy-4-aminopiperidines of formula (XIV-a), may be
- 30 obtained, for example, by catalytic hydrogenation of an imine of formula (XVI-a) and subsequently transforming the secondary amine of formula (XV-a) into the 3-methoxy-

4-aminopiperidines of formula (XIV-a) by hydrogenolysis. The imines of formula (XVI-a) may be prepared following art-known imine formation procedures starting from a 3-methoxy-4-oxo-piperidine of formula (XVII-a) and an amine of formula (XVIII).



In the intermediates of formula (XVIII), (XVI-a) and (XV-a), R⁷ is hydrogen, C₁₋₆alkyl or hydroxyC₁₋₆alkyl and Ar is phenyl optionally substituted with halo, C₁₋₆alkyl, C₁₋₆alkyloxy; or naphthyl optionally substituted with halo, C₁₋₆alkyl, C₁₋₆alkyloxy.

The reactionsequence starting from an intermediate of formula (XVII-a) up to an intermediate of formula (XIV-a) may also be performed as a one-pot procedure.

Enantiomerically enriched or enantiomerically pure intermediates of formula (XV-a) and (XIV-a) may be prepared according to one of the following methods.

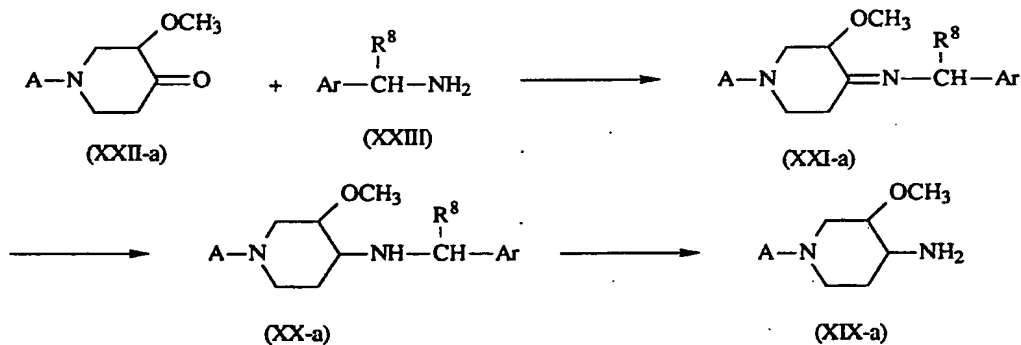
The starting racemic 3-methoxy-4-oxo-piperidine of formula (XVII-a) or the corresponding ketal such as, for example, a diC₁₋₆alkylketal, e.g. 4,4-diethoxy-3-methoxypiperidine, may be separated into its enantiomers and further converted into an enantiomerically pure cis-3-methoxy-4-aminopiperidine of formula (XIV-a) as described hereinabove. Said separation in enantiomers can be performed, for instance, by column chromatography using a chiral stationary phase, e.g. Chiracell OD.

Alternatively, the intermediate imine of formula (XVI-a) can be prepared using one of the enantiomers of a chiral amine of formula (XVIII), wherein R⁷ is defined as hereinabove but other than hydrogen, said amines being represented by (XVIII-b), e.g. (-)-(R)-α-aminobenzene-ethanol or (+)-S-α-aminobenzeneethanol, which after hydrogenation yields diastereomeric amines of formula (XV-a), which may be conveniently separated by physical separation methods such as selective crystallization or chromatographic techniques. Hydrogenolysis of the arylmethylgroup (Ar-CH(R⁷)-)

from the respective diastereomeric amines of formula (XV-a) yields the respective enantiomeric 3-methoxy-4-aminopiperidines of formula (XIV-a).

Yet another way of obtaining enantiomerically pure 3-methoxy-4-aminopiperidines of formula (XIV-a) was found during the optimization of the above reaction sequence.

- 5 When one reacts a racemic ketone such as a 3-methoxy-4-oxo-piperidine of formula (XXII-a) with an enantiomerically pure chiral amine of formula (XXIII-b), e.g. (-)-(S)- α -methylbenzylamine, and subsequently hydrogenates the thus formed imine of formula (XXI-a), one would expect a ratio of diastereomeric amines of formula (XV-a) of approximately 1:1. Unexpectedly, however, it was found that after the above
- 10 reaction sequence said diastereomeric ratio differs substantially from the ratio 1:1. In other words, the amines of formula (XV-a) were diastereomerically enriched or even diastereomerically pure. Hence, in the course of this reaction sequence one diastereomer is converted into the other by configurational inversion of the stereocenter bearing the methoxygroup.
- 15 Thus, a novel and inventive way to obtain novel enantiomerically enriched or enantiomerically pure 3-methoxy-4-aminopiperidines of formula (XIV-a) and more in general intermediates of formula (XIX-a) was found following the procedure described in more detail hereinunder.



20

- In (XIX-a), (XX-a), (XXI-a) and (XXII-a) the radical A represents hydrogen, $-(\text{CH}_2)_n-\text{NH}_2$, $-(\text{CH}_2)_n-\text{NH}-\text{P}$, P^1 or L, wherein n, P, P^1 and L are as defined hereinabove. A racemic mixture of 3-methoxy-4-oxo-piperidine of formula (XXII-a)
- 25 may be reacted with one enantiomer of a chiral amine of formula (XXIII), wherein R^8 is C_1 -alkyl or hydroxy C_1 -alkyl, Ar is phenyl optionally substituted with halo, C_1 -alkyl, C_1 -alkyloxy; or naphthyl optionally substituted with halo, C_1 -alkyl, C_1 -alkyloxy; yielding a diastereomeric mixture of the intermediate imine of formula (XXI-a). Said reaction may be carried out using art-known imine-formation procedures, such as, for
- 30 instance, stirring the reactants at reflux temperature in a reaction-inert solvent such as,

for example, an aromatic hydrocarbon, e.g. methylbenzene, using a Dean-Stark apparatus.

The imine of formula (XXI-a) may be isolated and, if necessary, purified, for instance by column chromatography, distillation or crystallization. Subsequently the imine may be hydrogenated by stirring the imine under hydrogen atmosphere in a suitable solvent such as, for example, an alcohol, e.g. methanol or ethanol; an ether, e.g. tetrahydrofuran or 2,2'-oxybispropane; an ester, e.g. ethylacetate; an aromatic hydrocarbon, e.g. methylbenzene; in the presence of appropriate catalysts, e.g. palladium-on-charcoal, platinum-on-charcoal, rhodium-on carbon and the like, yielding a diastereomerically enriched or diastereochemically pure amine of formula (XX-a).

Alternatively, the intermediate imine of formula (XXI-a) is not isolated. In this case a racemic mixture of a 3-methoxy-4-oxo-piperidine of formula (XXII-a) is reacted with one of the enantiomers of a chiral amine of formula (XXIII) under hydrogenation conditions, yielding diastereomerically enriched or diastereomerically pure intermediate amines of formula (XX-a). Said reaction is performed in analogous reaction conditions as described hereinabove. However in this case, the reaction preferably is performed in admixture with an acid, such as, acetic acid, oxalic acid, chloroacetic acid, 2-hydroxy-1,2,3-propanetricarboxylic acid, and in particular (-) [S-(R*,R*)]-2,3-dihydroxy-butanedioic acid, especially when the solvent is an alcohol.

In the amines of formula (XXIII), R⁸ is suitably hydroxymethyl, methyl or ethyl, especially methyl and Ar is preferably an unsubstituted phenyl or naphthyl, especially phenyl. Preferred amines of formula (XXIII) are the enantiomers of α -methylbenzylamine, i.e. (-)-(S)- α -methylbenzylamine or (+)-(R)- α -methylbenzylamine.

Sometimes, during the hydrogenation reaction a small amount of trans-3-methoxy-4-aminoderivative can be formed, which may be removed by crystallization or chromatography.

A preferred way of preparing a diastereomerically enriched or pure amine of formula (XX-a) is first preparing an imine of formula (XXI-a) with one enantiomer of α -methylbenzylamine and subsequently hydrogenating the imine of formula (XXI-a) by stirring it in methylbenzene under a hydrogen atmosphere using a rhodium catalyst.

In order to avoid the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g. thiophene, quinoline-sulphur and the like. Higher pressures and/or temperatures may enhance the reaction rate.

The resulting intermediate of formula (XX-a) has a diastereomeric ratio, that differs very much from the 1:1 ratio. In other words, the intermediate of formula (XX-a) is diastereomerically enriched or diastereomerically pure. The respective diastereomeric

forms may then, if necessary, be further separated using conventional physical methods such as chromatography or fractional crystallization optionally after salt formation. The thus obtained diastereomerically pure amines of formula (XX-a) may then be further hydrogenolyzed, removing the chiral auxiliary group $\text{Ar-CH(R}^8\text{)-}$, yielding
5 enantiomerically pure 3-methoxy-4-aminopiperidines of formula (XIX-a).

It is noteworthy that the configuration of the stereocenter bearing the methoxy group is determined by the configuration of the enantiomerically pure amine of formula (XVIII) that is used. Hence, either configuration of said stereocenter can be obtained by selection
10 of one or the other enantiomer of the amine of formula (XXIII). It may further be noted that the choice of the acid used during the hydrogenation of the imine, can also influence up to a certain degree the diastereomeric ratio of the amines of formula (XIX-a). The choice of catalyst can also influence up to a certain degree the amount of trans-4-amino-3-methoxy derivative that is formed.

The diastereomerically enriched or diastereomerically pure intermediates of formula (XX-a) and the enantiomerically enriched or enantiomerically pure intermediates of formula (XIX-a) and the pharmaceutically acceptable acid addition salts thereof are deemed novel. Also the enantiomerically enriched or enantiomerically pure intermediates
20 of formula (II-a), (IV-a), (VII-a), (X-a), (XIII-a), (XIV-a) and the pharmaceutically acceptable acid addition salts are also deemed novel. Said intermediates may be prepared as described hereinabove starting from enantiomerically enriched or enantiomerically pure intermediates of formula (XIV-a).

In this way and starting from enantiomerically enriched or enantiomerically pure intermediates described hereinabove a novel and inventive way to prepare enantiomerically enriched or enantiomerically pure compounds of formula (I-a), especially, the laevo-rotatory enantiomers of the compounds of formula (I-a) is
25 provided.

It is evident that the cis and trans diastereomeric racemates of the compounds of formula (I), (I-a), or any of the other intermediates may also be resolved into their optical isomers, cis(+), cis(-), trans(+) and trans(-) by the application of art-known methodologies. Diastereoisomers may be separated by physical separation methods
30 such as selective crystallization and chromatographic techniques, e.g. counter current distribution, and enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with enantiomerically pure acids or their enantiomerically pure derivatives.

The compounds of formula (I), the pharmaceutically acceptable salts and stereoisomeric forms are 5-HT₃-receptor antagonists, as demonstrated by the fact that they have been found active, for example, in antagonising the von Bezold-Jarish chemoreflex evoked by serotonin in rats (Pharmacology and Toxicology, 70, Supp II, 17-22 (1992)). This test is described hereinafter as example 10.

The compounds of formula (I), especially the compounds of formula (I-a), are active during a long period of time. Moreover, the present compounds of formula (I), especially the compounds of formula (I-a), show a high degree of cardiovascular safety.

In view of their 5-HT₃-antagonistic activity the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare these pharmaceutical compositions, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is intimately mixed with a pharmaceutically acceptable carrier. Said carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form; in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of the

compounds of formula (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.

- 5 Dosage unit form as used in the specification herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable
10 solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

- In view of their 5-HT₃-antagonising activity the compounds of formula (I) and especially the novel compounds of formula (I-a) are useful in the treatment of 5-HT₃-
15 mediated disorders such as anxiety, psychosis, depression (Arzneim. Forsch., 42(1), 239-246 (1992)), schizophrenia, cognitive disorders, e.g. memory impairment (Arzneim. Forsch., 42(1), 246-249 (1992)), drug abuse, migraine, emesis, e.g. cytotoxic drug and radiation induced emesis (Drugs 42(4), 551-568 (1991)), irritable
20 bowel syndrome, especially diarrheapredominant irritable bowel syndrome, and related disorders. Consequently, the present invention provides a method of treating warm-blooded animals suffering from 5-HT₃-mediated diseases such as anxiety, psychosis, depression, schizophrenia, cognitive disorders, e.g. memory impairment, drug abuse, migraine, emesis, e.g. cytotoxic drug and radiation induced emesis, irritable bowel
25 syndrome, especially diarrheapredominant irritable bowel syndrome, and related disorders. Said method comprises the systemic administration of an effective 5-HT₃-antagonistic amount of a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereoisomeric form thereof, to warm-blooded animals.

- The present compounds of formula (I) are useful for the manufacture of a medicament for treating 5-HT₃ mediated diseases. The novel compounds of formula
30 (I-a) are useful as a medicine.

- In general it is contemplated that an effective amount would be from about 0.001 mg/kg to about 50 mg/kg body weight, preferably from about 0.02 mg/kg to about 5 mg/kg body weight. A method of treatment may also include administering the active
35 ingredient on a regimen of between two or four intakes per day.

Experimental partA. Preparation of the intermediatesExample 1

- 5 a) 3,4,4-trimethoxy-1-(phenylmethyl)piperidine (0.676 mol) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated. This residue (mixture of enantiomers) was separated in its enantiomers by column chromatography over a Chiracell OD column (eluent: hexanes/2-propanol 98.5/1.5). The fraction, corresponding to a first chromatographic peak, was collected and the solvent was evaporated. A sample was
- 10 purified by distillation (bp at 0.5 mmHg: 120°C), yielding: 56 g of (-)-3,4,4-trimethoxy-1-(phenylmethyl)piperidine $[\alpha]_{20}^D = -54.00^\circ$ (c = 0.5% in methanol) (interm. 1).

- The fraction, corresponding to a second chromatographic peak, was collected and the solvent was evaporated. A sample was purified by distillation (bp at 0.5 mmHg: 120°C), yielding 64 g of (+)-3,4,4-trimethoxy-1-(phenylmethyl)piperidine; $[\alpha]_{20}^D =$
- 15 49.60° (c = 0.5% in methanol) (interm. 2).

- b) A mixture of intermediate (1) (0.21 mol) in methanol (600 ml) was hydrogenated at 50°C with palladium-on-charcoal 10% (3g) as a catalyst. After uptake of H₂ (1 equiv), the catalyst was filtered off. Calcium oxide (0.63 mol) was added to the filtrate. The reaction mixture was stirred at room temperature. Ethyl chloroformate (0.63 mol) was
- 20 added dropwise. The reaction mixture was stirred for 2 hours at 50°C. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated. Methylbenzene was added to the residue. The suspension was filtered and the filtrate was evaporated. The residue was purified by distillation, yielding 32.6 g (63%) of (-)-ethyl 3,4,4-trimethoxy-1-piperidinecarboxylate; $[\alpha]_{20}^D = -39.40^\circ$ (c = 0.5% in
- 25 methanol) (interm. 3).

- c) A mixture of interm. (3) (0.132 mol), 4-methylbenzenesulfonic acid (0.6 g) in 2-propanone (180 ml) and water (30 ml) was stirred and refluxed for 18 hours. The reaction mixture was cooled and N,N-diethylethanamine (0.6 ml) was added. The solvent was evaporated (temperature was kept < 40°C). The residue was dissolved in
- 30 CH₂Cl₂. This solution was washed twice with a saturated NaCl solution. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by distillation, yielding 19.2 g (-)-ethyl 3-methoxy-4-oxo-1-piperidine-carboxylate (72.3%); $[\alpha]_{20}^D = -44.40^\circ$ (c = 0.5% in methanol) (interm. 4).

- d) A mixture of intermediate (4) (0.095 mol) and benzenemethanamine (0.11 mol) in
- 35 methanol (200 ml) was hydrogenated under atmospheric conditions with palladium on

- activated charcoal 10% (2 g) as a catalyst in the presence of 4% solution of thiophene in 2,2'-oxybispropane (2 ml). After uptake of hydrogen, the catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in methanol (250 ml) and the resulting mixture was hydrogenated at 50°C with palladium on activated charcoal 10% (2 g) as a catalyst. After uptake of hydrogen (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by distillation (bp at 0.1 mm Hg: 85°C), yielding 13.4 g (70%) ethyl (-)-cis-4-amino-3-methoxy-1-piperidinecarboxylate; $[\alpha]_{20}^D = -78.9^\circ$ (c = 1% in methanol) (interm. 5).

- In a similar manner but starting from intermediate (2) was also prepared :
 10 (+)-ethyl cis-4-amino-3-methoxy-1-piperidinecarboxylate; $[\alpha]_{20}^D = -80.64^\circ$ (c = 0.6% in methanol) (interm. 6).

Example 2

- 15 a) A mixture of ethyl 3-methoxy-4-oxo-1-piperidinecarboxylate (0.5 mol), (-)-(S)- α -methylbenzenemethanamine (0.53 mol), 4-methylbenzenesulfonic acid monohydrate (1.25g) and methylbenzene (625ml) was stirred and refluxed with a Dean-Stark apparatus for 3 hours. The reaction mixture was evaporated and distilled, yielding 121 g (79.5%) of (-)-ethyl [cis(S)]-3-methoxy-4-[(1-phenylethyl)imino]-1-piperidinecarboxylate (interm. 7).
- 20 b) A mixture of intermediate (7) (0.4 mol) and methylbenzene (750 ml) was hydrogenated at room temperature and atmospheric pressure with rhodium-on-carbon (5 g) as a catalyst. After uptake of hydrogen (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in 4-methyl-2-pentanone and converted into the 4-methylbenzenesulfonic acid salt (1:1) with 4-methylbenzenesulfonic acid monohydrate (1 eq.). The salt was filtered off and dried. This fraction was
- 25 recrystallized twice from a mixture of 2,2'-oxybispropane/methanol (250 ml/180 ml). The precipitated product was filtered off and dried, yielding 61.7 g (32.5%) of (-)-ethyl [cis(S)]-3-methoxy-4-[(1-phenylethyl)amino]-1-piperidinecarboxylate 4-methylbenzenesulfonate (1:1); $[\alpha]_{20}^D = -62.16^\circ$ (c = 1% in methanol) (interm. 8).
- 30 In a similar manner, but using (+)-(R)- α -methylbenzene methanamine was prepared :
 (+)-ethyl [cis, (R)]-3-methoxy-4-[(1-phenylethyl)amino]-1-piperidinecarboxylate 4-methylbenzenesulfonate (1:1); $[\alpha]_{20}^D = 62.79^\circ$ (c = 1% in methanol) (interm. 9).

Example 3

- 35 a) A mixture of ethyl 3-methoxy-4-oxo-1-piperidinecarboxylate (0.2 mol), (-)-(S)- α -methylbenzenemethanamine (0.4 mol) and (-)-[S-(R*,R*)] 2,3-dihydroxybutanedioic acid

- (0.2 mol) in methanol (500 ml) was hydrogenated at room temperature and atmospheric pressure with palladium on activated charcoal 10% (2 g) as a catalyst, in the presence of a 4% solution of thiophene in 2,2'-oxybispropane (2 ml). After uptake of H₂ (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue was partitioned
- 5 between methylbenzene and H₂O/NH₄OH. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was dissolved in 4-methyl-2-pentanone and converted into the 4-methylbenzenesulfonic acid salt (1:1) with 4-methylbenzenesulfonic acid . monohydrate (1 eq.). The salt was filtered off and dried. This fraction was recrystallized from 2,2'-oxybispropane/CH₃OH (500 ml/100 ml). The
- 10 mixture was stirred for 24 hours. The precipitate was filtered off and dried (vacuum; 50°C), yielding 32 g of (-)-ethyl [cis,(S)]-3-methoxy-4-[(1-phenylethyl)amino]-1-piperidinecarboxylate 4-methylbenzenesulfonate (1:1); $[\alpha]_{20}^D = -61.6^\circ$ (c = 0.5% in methanol) (interm. 8).
- In a similar manner, but using (+)-(R)- α -methylbenzene methanamine, was also prepared :
- 15 (+)-ethyl [cis, (R)]-3-methoxy-4-[(1-phenylethyl)amino]-1-piperidinecarboxylate 4-methylbenzenesulfonate (1:1) (interm. 9).
- b) Intermediate (8) (0.067 mol) was converted into the free base with aqueous ammonia. This mixture was extracted with methylbenzene. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residual free
- 20 base was dissolved in methanol (250 ml) and hydrogenated at room temperature and atmospheric pressure with palladium on activated charcoal 10% (2 g) as a catalyst. After uptake of H₂ (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by distillation (boiling point at 0.1 mm Hg: 85°C), yielding 9.9 g (79.2%) of ethyl (-)-cis-4-amino-3-methoxy-1-piperidinecarboxylate (interm. 5).
- 25 In a similar manner, but starting from intermediate (9), was also prepared : (+)-ethyl cis-4-amino-3-methoxy-1-piperidinecarboxylate (interm. 6).

Example 4

- a) A mixture of 53.3 g of ethyl 3-methoxy-4-oxo-1-piperidinecarboxylate (described in
- 30 EP-patent 76.350), 33 g of (-)-(R)- α -aminobenzeneethanol and 700 ml of ethanol was refluxed overnight. After cooling, the reaction mixture was evaporated and the residue was distilled, yielding 59.1 g (92%) of ethyl (R)-4-[(2-hydroxy-1-phenylethyl)imino]-3-methoxy-1-piperidinecarboxylate; bp. 180°C (pressure = 3.75.10⁻⁴ Pa) (interm. 10).
- b) A solution of 59.1 g of intermediate (10) in 500 ml of ethanol was hydrogenated at
- 35 normal pressure and at room temperature with 2 g of platinum-on-charcoal catalyst. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and

the filtrate was evaporated. The residue was purified over NH₂-silicagel (eluent CH₂Cl₂ / cyclohexane / methanol 60:40:0.5). The pure fractions were collected and the eluent was evaporated, yielding 18 g (30%) of ethyl (-)-[4(R),cis]-4-[(2-hydroxy-1-phenylethyl)amino]-3-methoxy-1-piperidinecarboxylate as a residue;

5 $[\alpha]_{20}^D = -96.70^\circ$ (c = 0.5% in methanol) (interm. 11).

c) A solution of 18 g of intermediate (11) in 250 ml of methanol was hydrogenated at normal pressure and at room temperature with 2 g of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was distilled, yielding 6.2 g (55%) of
10 ethyl (-)-cis-4-amino-3-methoxy-1-piperidinecarboxylate (interm. 5).

Example 5

a) 4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxylic acid (described in EP-0,389,037) (0.05 mol) was dissolved in a mixture of N,N-diethylethanamine
15 (7 ml) and trichloromethane (250 ml). Ethyl carbonochloridate (0.05 mol) was added dropwise at <10°C. The reaction mixture was stirred for 30 min at <10°C. The mixture was added to a solution of intermediate (5) (0.047 mol) in trichloromethane (250 ml), stirred at 10°C. The reaction mixture was stirred for 30 min at room temperature. The reaction mixture was washed with water, 5% NaOH and again water. The organic layer
20 was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated, yielding 19 g (94%) of (+)-ethyl cis-4-[(4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofuranyl)-carbonylamino]-3-methoxy-1-piperidinecarboxylate (interm. 12).

b) A mixture of intermediate (12) (0.045 mol) and potassium hydroxide (0.45 mol) in 2-propanol (300 ml) was stirred and refluxed for 12 hours. The reaction mixture was cooled and the solvent was evaporated. Water (100 ml) was added to the residue. The solvent was evaporated. The residue was partitioned between dichloromethane and water. The organic layer was separated, washed with water, dried (MgSO₄), filtered
30 and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/(CH₃OH/NH₃) 97/3). The pure fractions were collected and the solvent was evaporated. The residue was dried (vacuum; 50°C), yielding: 12.5 g (+)-cis-4-amino-5-chloro-2,3-dihydro-N-(3-methoxy-4-piperidiny)-2,2-dimethyl-7-benzofurancarboxamide (77.2%); $[\alpha]_{20}^{365} = 33.40^\circ$ (c = 0.5% in methanol) (interm.

35 13).

Example 6

- a) A mixture of intermediate (13) (0.017 mol), ethyl (2-chloroethyl)carbamate (0.02 mol) and *N,N*-diethylethanamine (0.022 mol) in *N,N*-dimethylformamide (150 ml) was stirred for 72 h at 70°C. The reaction mixture was cooled and the solvent was
5 evaporated. The residue was partitioned between dichloromethane and water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 97/3). The pure fractions were collected and the solvent was evaporated, yielding: 5 g (+)-ethyl
10 cis-[2-[4-[(4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofuranyl)carbonyl]-amino]-3-methoxy-1-piperidinyl]ethyl]carbamate (63%); $[\alpha]_{20}^D = 1.20^\circ$ (c = 0.5% in methanol) (interm. 14).
- b) A mixture of intermediate (14) (0.0106 mol) and potassium hydroxide (0.106 mol) in 2-propanol (45 ml) was stirred and refluxed for 4 hours. The mixture was cooled. The solvent was evaporated and the residue was stirred in water, then evaporated again. The
15 residue was dissolved in dichloromethane and this solution was washed with a small volume of water, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH/(CH₃OH/NH₃) 90/9/1). The pure fractions were collected and the solvent was evaporated, yielding 3.2 g (76%) (-)-cis-4-amino-*N*-[1-(2-aminoethyl)-3-methoxy-4-piperidinyl]-5-chloro-2,3-
20 dihydro-2,2-dimethyl-7-benzofurancarboxamide; $[\alpha]_{20}^D = -1.50^\circ$ (c = 0.2% in methanol) (interm. 15).

Example 7

- a) A mixture of intermediate (13) (0.023 mol) and 2-propenenitrile (0.028 mol) in
25 2-propanol (150 ml) was stirred and refluxed for 16 hours. The reaction mixture was cooled and the solvent was evaporated, yielding 8 g (85.5%) (-)-cis-4-amino-5-chloro-*N*-[1-(2-cyanoethyl)-3-methoxy-4-piperidinyl]-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxamide; $[\alpha]_{20}^D = -1.60^\circ$ (c = 0.5% in methanol) (interm. 16).
- b) A mixture of intermediate (16) (0.02 mol) in methanol (250 ml) and tetrahydrofuran
30 (100 ml) was hydrogenated under atmospheric conditions with Raney nickel (3 g) as a catalyst. After uptake of hydrogen (2 equiv), the catalyst was filtered off and the filtrate was evaporated, yielding 7 g (85.2%) (-)-cis-4-amino-*N*-[1-(3-aminopropyl)-3-methoxy-4-piperidinyl]-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxamide
(interm. 17).

Example 8

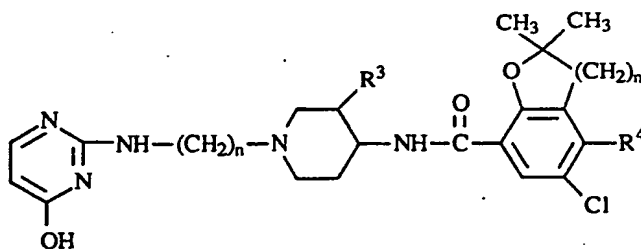
- a) Intermediate (17) (0.769 mol) was dissolved in 1-butanol (2310 ml) (heating to 50 °C required). Potassium carbonate (1.538 mol) was added at 30 °C (heterogeneous). 2-Chloro-4-methoxypyrimidine (0.960 mol) was added and the reaction mixture was heated to reflux temperature (104 °C). The reaction mixture was stirred and refluxed for 11 hours. The mixture was allowed to cool to 20 °C. Water (769 ml) was added and the mixture was stirred for 15 minutes. The layers were separated. The organic layer was evaporated (1.66 mm Hg ; 60 °C), yielding 458.9 g (92.1%) of (±)-cis-4-amino-5-chloro-2,3-dihydro-N-[3-methoxy-1-[3-[(4-methoxy-2-pyrimidinyl)amino]propyl]-4-piperidinyl]-2,2-dimethyl-7-benzofurancarboxamide (interm. 18).
- b) Hydrochloric acid in 2-propanol (434 ml) was added dropwise over a 15-minutes period to a solution of intermediate (18) (0.769 mol) in 4-methyl-2-pentanone (3845 ml), stirred at 15-20 °C (cooling on ice bath was required). The reaction mixture was stirred for 1 hour at 15 °C. The precipitate was filtered off, washed with 4-methyl-2-pentanone (769 ml) and dried (vacuum; 50 °C), yielding 425.9 g (93.6%) of (±)-cis-4-amino-5-chloro-2,3-dihydro-N-[3-methoxy-1-[3-[(4-methoxy-2-pyrimidinyl)amino]propyl]-4-piperidinyl]-2,2-dimethyl-7-benzofurancarboxamide dihydrochloride (interm. 19)

B. Preparation of the final compoundsExample 9

- A mixture of intermediate (17) (0.017 mol) and 2-methylthio-4-pyrimidinone (0.022 mol) in acetonitrile (300 ml) was stirred and refluxed for 16 hours. Extra 2-methylthio-4-pyrimidinone (2 g) was added and the reaction mixture was stirred and refluxed for 16 hours. The reaction mixture was cooled. The solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH/(CH₃OH/NH₃) 90/9/1). The pure fractions were collected and the solvent was evaporated. The residue was triturated in 2, 2'-oxybispropane. The solid was filtered off and dried (vacuum; room temperature), yielding 2.65 g (29.7%) (-)-cis-4-amino-5-chloro-2,3-dihydro-N-[1-[3-[(3,4-dihydro-4-oxo-2-pyrimidinyl)amino]propyl]-3-methoxy-4-piperidinyl]-2,2-dimethyl-7-benzofurancarboxamide; mp. 164.3°C; $[\alpha]_{20}^D = -17.54^\circ$ (c = 1% in methanol) (comp. 1).

In this manner there were prepared :

Table 1



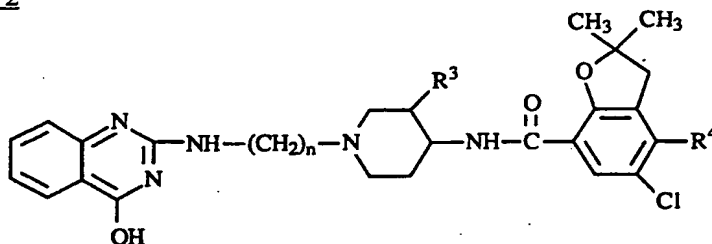
Co. No.	R ³	R ⁴	n	m	physical data
1	OCH ₃	NH ₂	3	1	cis; mp. 164.3°C; $[\alpha]_{20}^D = -17.54^\circ$ (c = 1% in methanol)
2	OCH ₃	NH ₂	2	1	cis; mp. 179.9°C, $[\alpha]_{20}^{365} = -156.45^\circ$ (c=0.1% in CH ₃ OH)
3	OCH ₃	NH ₂	3	1	cis; mp. 164.3°C, $[\alpha]_{20}^D = 17.21^\circ$ (c=1% in CH ₃ OH)
4	OCH ₃	NH ₂	2	1	cis; $[\alpha]_{20}^{365} = 158.53^\circ$ (c=0.1% in CH ₃ OH)
5	OCH ₃	NH ₂	3	1	cis; 2.5 H ₂ O / mp. 163.8°C
6	OCH ₃	NH ₂	2	1	cis; mp. 198.8°C
7	H	NH ₂	2	1	mp. 204.4°C
8	H	NH ₂	3	1	H ₂ O / mp. 165.8°C
9	H	NH ₂	3	2	mp. 221.1°C
10	H	H	2	1	mp. 126.9°C
11	H	H	3	2	mp. 106.1°C

Example 10

- 5 A mixture of 4.15 g of 2-chloro-4-hydroxyquinazoline, 4.57 g of 4-amino-N-[1-(3-aminopropyl)-4-piperidiny]-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxamide (described in EP-0, 445, 862) and 0.80 g of calcium oxide was stirred for 1 hour at 140 °C. The reaction mixture was dissolved in a mixture of dichloromethane and methanol. The whole was washed with water, dried, filtered and evaporated. The
- 10 residue was purified twice by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH(NH₃) 90:10 ; CH₂Cl₂ / CH₃OH(NH₃) 88:12). The eluent of the desired fraction was evaporated and the residue was boiled in 2,2'-oxybispropane. The product was filtered off and dried, yielding 3.2 g (50.8%) of 4-amino-5-chloro-2,3-dihydro-N-[1-[3-[(4-hydroxy-2-quinazolinyl)amino]propyl]-4-piperidiny]-2,2-dimethyl-7-
- 15 benzofurancarboxamide; mp. 159.6 °C (comp. 12).

In this manner there were prepared :

Table 2



5

Co. No.	R ³	R ⁴	n	physical data
12	H	NH ₂	3	mp. 159.6°C
13	H	NH ₂	4	mp. 152.3°C
14	H	NH ₂	2	mp. 160°C (decomp.)
15	OCH ₃	NH ₂	3	cis / 1/2 H ₂ O / mp. 185.6°C
16	OCH ₃	-NH-CO-CH ₃	3	cis; H ₂ O/mp. 181.2°C
17	OCH ₃	H	3	cis; mp. 140.5°C
18	OCH ₃	H	2	cis; mp. 150.0°C
19	H	H	2	mp. 238.1°C
20	H	H	3	mp. 131.1°C

Example 11

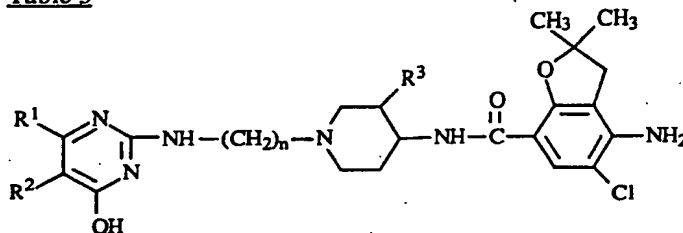
10 A mixture of 2.6 g of 2,6-dichloro-4-quinazolinol (described in J.Med.Chem., 1968, p.130), 3.7 g of 4-amino-N-[1-(2-aminoethyl)-4-piperidiny]-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxamide (described in EP-0, 445, 862), 0.8 g of calcium oxide and 5.64 g of N,N-dimethylacetamide was stirred for 3 hours at 140°C. After cooling, the reaction mixture was evaporated and the residue was taken up in a mixture of dichloromethane and methanol. The whole was washed with water. The partly

15 precipitated product was filtered off (first fraction). The organic layer was decanted, dried, filtered and evaporated (second fraction). The combined fractions were purified twice by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH(NH₃) 95:5 ; CH₂Cl₂ / CH₃OH 92:8). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. At 0°C, the product was filtered off and dried in vacuo at

20 60°C, yielding 1 g (18.3%) of 4-amino-5-chloro-N-[1-[2-[(6-chloro-4-hydroxy-2-quinazolinyl)amino]ethyl]-4-piperidiny]-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxamide; mp. 206.6°C (comp. 21).

In this manner there were prepared :

Table 3



5

Co. No.	R ¹ , R ²	R ³	n	physical data
21	-CH=CH-C(Cl)=CH-	H	2	mp. 206.6°C
22	-CH=C(Cl)-CH=CH-	H	2	mp. 242.4°C
23	-CH=C(Cl)-CH=CH-	OCH ₃	3	mp. 215.5°C; cis
24	-CH=CH-C(Cl)=CH-	OCH ₃	3	1/2 H ₂ O/mp. 237.9°C; cis

Example 12

Water (2880 ml) was added to intermediate (19) (0.72 mol, resulting in complete dissolution of intermediate (19). Hydrochloric acid (193 ml) was added dropwise. The reaction mixture was heated to reflux temperature (95 °C). The reaction mixture was stirred and refluxed for 24 hours. More hydrochloric acid (128.6 ml) was added at reflux temperature. The reaction mixture was stirred and refluxed for 2.5 hours. Heating was stopped. Dichloromethane (360 ml) was added. The layers were separated. Dichloromethane (1080 ml) was added to the aqueous phase. At 20-25 °C, the biphasic mixture was alkalized with ammonium hydroxide (433 ml) (until pH > 10; addition over a 30-minutes period; external cooling required!; the mixture was homogeneous at start, precipitation resulted at pH = 6-7 and dissolved at higher pH). The layers were separated. The aqueous layer was extracted with dichloromethane (360 ml). The organic extracts were combined, dried, filtered and evaporated (vacuum; 40 °C). The residue was dried (vacuum; 40 °C), yielding 321.2 g (88.3%) of (-)-*cis*-4-amino-5-chloro-N-[1-[3-[(3,4-dihydro-4-oxo-2-pyrimidinyl)amino]propyl]-3-methoxy-4-piperidinyl]-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxamide (comp. 1).

C. Pharmacological example

25 Example 13 : von Bezold-Jarish test

Male spontaneous hypertensive rats (± 6 months) were anaesthetized by ether inhalation and the femoral vein and artery were dissected and cannulated with polyethylene

catheters. Lidocaine (20%) was administered to the wound around the cannulas to induce local analgesia.

- The animals were restrained in Bollman cages, and the arterial catheter was connected to a strain gauge blood pressure transducer and systolic pressure was analysed. When the animals were fully awake a control injection of serotonin (0.04 mg/kg) was given via the femoral vein catheter. The response of the systolic blood pressure to a intravenous serotonin injection normally evolves in three phases : 1) a short and sharp decrease (von Bezold-Jarish reflex), 2) an increase and 3) a longer lasting decrease in systolic blood pressure. Inhibition of the first sharp decrease in blood pressure (von Bezold-Jarish reflex) is taken as a measure for 5-HT₃-antagonism. Some time after the control injection of serotonin the test compound was injected intraperitoneally. After 30 minutes serotonin was again injected intravenously and the presence or absence of the first short and sharp decrease was recorded. The same procedure was repeated after 60 minutes. The compounds were tested at different doses.
- 15 The Lowest Active Dose (LAD) which is shown in Table 4 may be defined as the dose (in mg/kg body weight) at which at least half of the animals tested show inhibition of the von Bezold-Jarish reflex.

Table 4

Co. No.	LAD (mg/kg)
5	0.04
7	0.04
9	0.16
12	0.16
14	0.01
19	0.01
21	0.16
11	0.16
8	0.04
24	0.16
23	0.16
16	0.16
17	0.04
6	0.01
10	0.01
1	0.04
2	0.04

D. Composition Examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 14 : Oral solutions

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution is filled in suitable containers.

Example 15 : Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I..

Example 16 : Film-coated tablets

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is

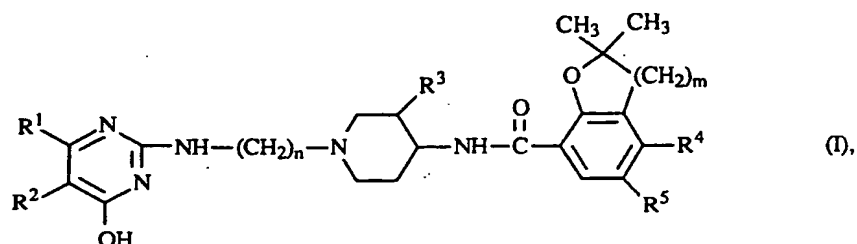
molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added

2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole is homogenated. The tablet cores are coated with

5 the thus obtained mixture in a coating apparatus.

Claims

1. Use of a compound of formula



a pharmaceutically acceptable acid addition salt form or a stereochemically isomeric form thereof, wherein

R^1 and R^2 represent hydrogen, or

R^1 and R^2 taken together form a bivalent radical of formula

10 $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ (a),

$-\text{CH}=\text{C}(\text{Cl})-\text{CH}=\text{CH}-$ (b) or

$-\text{CH}=\text{CH}-\text{C}(\text{Cl})=\text{CH}-$ (c);

n represents 2, 3 or 4;

R^3 represents hydrogen or methoxy;

15 m represents 1 or 2;

R^4 represents hydrogen, amino or C_{1-3} alkylcarbonylamino; and

R^5 represents hydrogen or halo,

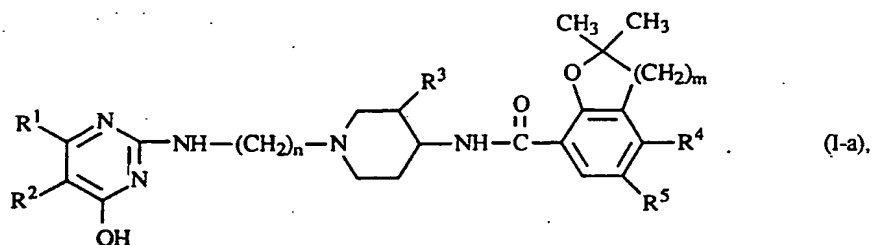
for the manufacture of a medicament for treating 5-HT₃-mediated disorders.

20 2. A use according to claim 1, wherein R^3 represents methoxy and has the cis-configuration.

3. A use according to claim 2, wherein the compound is laevo-rotatory.

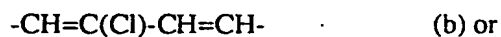
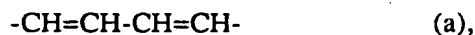
25 4. A use according to claim 1, wherein the compound is (-)-cis-4-amino-5-chloro-2,3-dihydro-N-[1-[3-[(3,4-dihydro-4-oxo-2-pyrimidinyl)amino]propyl]-3-methoxy-4-piperidinyl]-2,2-dimethyl-7-benzofurancarboxamide or (-)-cis-4-amino-5-chloro-N-[1-[2-[(3,4-dihydro-4-oxo-2-pyrimidinyl)amino]ethyl]-2,3-dihydro-3-methoxy-4-piperidinyl]-2,2-dimethyl-7-benzofurancarboxamide, or a pharmaceutically acceptable
30 acid addition salt form thereof.

5. A laevo-rotatory enantiomer of a compound of formula



or a pharmaceutically acceptable acid addition salt thereof, wherein R^1 and R^2 represent hydrogen, or

- 5 R^1 and R^2 taken together form a bivalent radical of formula



n represents 2 or 3;

- 10 R^3 represents methoxy and has the *cis*-configuration;

m represents 1 or 2;

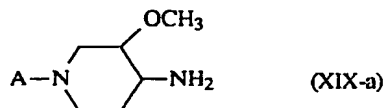
R^4 represents hydrogen, amino or C_{1-3} alkylcarbonylamino; and

R^5 represents hydrogen or halo.

- 15 6. A compound according to claim 5, wherein the compound is (-)-*cis*-4-amino-5-chloro-2,3-dihydro-N-[1-[3-[(3,4-dihydro-4-oxo-2-pyrimidinyl)amino]propyl]-3-methoxy-4-piperidinyl]-2,2-dimethyl-7-benzofurancarboxamide or (-)-*cis*-4-amino-5-chloro-N-[1-[2-[(3,4-dihydro-4-oxo-2-pyrimidinyl)amino]ethyl]-2,3-dihydro-3-methoxy-4-piperidinyl]-2,2-dimethyl-7-benzofurancarboxamide or a pharmaceutically acceptable acid addition salt form thereof.
- 20

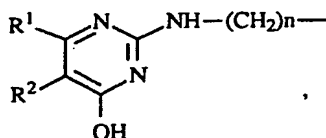
7. A pharmaceutical composition comprising an inert carrier and as an active ingredient an effective 5-HT₃-antagonistic amount of a compound as claimed in claim 5.

- 25 8. An enantiomerically enriched or enantiomerically pure *cis*-3-methoxy-4-amino-piperidine of formula



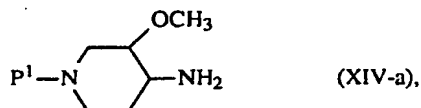
- 30 or a pharmaceutically acceptable acid addition salt thereof,

- wherein A is hydrogen, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-P$, P^1 or L, wherein P and P^1 each independently represent C_{1-4} alkylcarbonyl; C_{1-4} alkyloxycarbonyl; trihalomethylcarbonyl; diphenylmethyl; triphenylmethyl or arylmethyl, wherein aryl is phenyl optionally substituted with up to two substituents selected from C_{1-4} alkyloxy or halo; and L represents a radical of formula



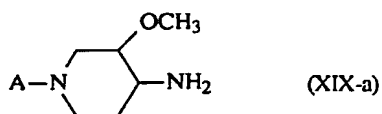
- wherein R^1 and R^2 represent hydrogen, or R^1 and R^2 taken together form a bivalent radical of formula
- 10 $-CH=CH-CH=CH-$ (a),
 $-CH=C(Cl)-CH=CH-$ (b) or
 $-CH=CH-C(Cl)=CH-$;
 and n represents 2, 3 or 4.

- 15 9. An intermediate as claimed in claim 8 wherein the intermediate is an enantiomerically enriched or enantiomerically pure cis-3-methoxy-4-aminopiperidine of formula



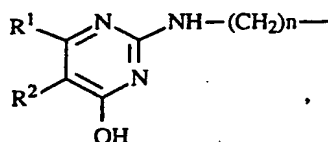
- 20 wherein P^1 is C_{1-4} alkylcarbonyl; C_{1-4} alkyloxycarbonyl; trihalomethylcarbonyl; diphenylmethyl; triphenylmethyl or arylmethyl, wherein aryl is phenyl optionally substituted with up to two substituents selected from C_{1-4} alkyloxy or halo; or an acid addition salt thereof.

- 25 10. A process of preparing an enantiomerically enriched or enantiomerically pure cis-3-methoxy-4-aminopiperidine of formula

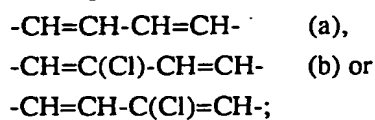


- 30 wherein A is hydrogen, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-P$, P^1 or L, wherein P and P^1 each independently represent C_{1-4} alkylcarbonyl; C_{1-4} alkyloxycarbonyl; trihalomethylcarbonyl; diphenylmethyl; triphenylmethyl or arylmethyl, wherein aryl is phenyl

optionally substituted with up to two substituents selected from C₁₋₄alkyloxy or halo; and L represents a radical of formula



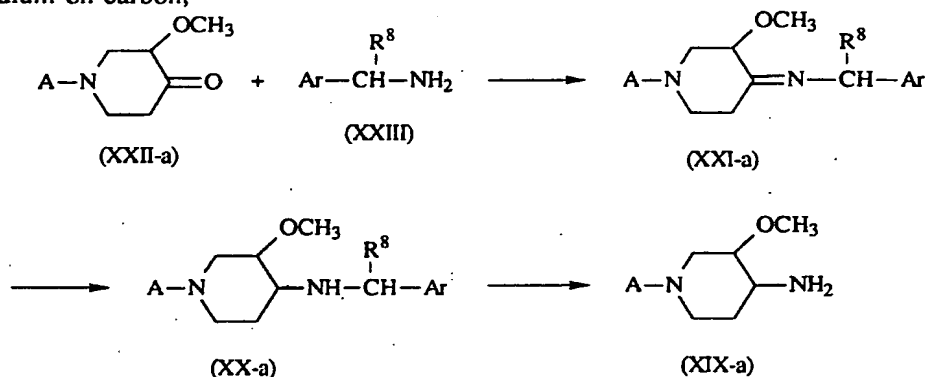
- 5 wherein R¹ and R² represent hydrogen, or R¹ and R² taken together form a bivalent radical of formula



- 10 and n represents 2, 3 or 4,

characterized by

reacting a racemic 3-methoxy-4-oxo-piperidine of formula (XXII-a) wherein A is as defined hereinabove, with one enantiomer of a chiral amine of formula (XXIII), wherein R⁸ is C₁₋₆alkyl or hydroxyC₁₋₆alkyl and Ar is phenyl optionally substituted with halo, C₁₋₆alkyl, C₁₋₆alkyloxy, or naphthyl optionally substituted with halo, C₁₋₆alkyl, or C₁₋₆alkyloxy; thus forming an intermediate of formula (XXI-a), which is hydrogenated in the presence of a catalyst, such as palladium-on-charcoal, platinum-on-charcoal, or rhodium-on-carbon;



20

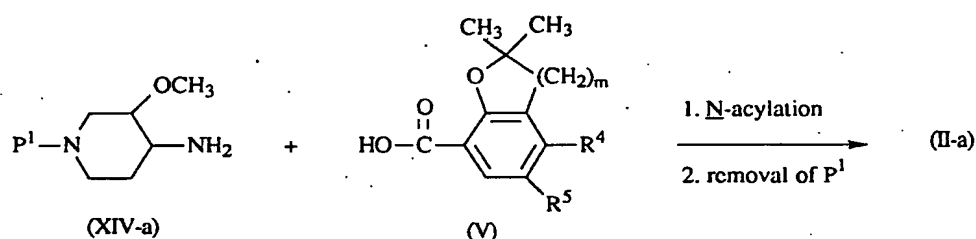
thus forming a diastereomerically enriched or diastereomerically pure intermediate of formula (XX-a) and subsequently removing the chiral auxiliary group Ar-CH(R⁸)-, and if desired, converting the intermediates of formula (XIX-a) into an acid addition salt form by treatment with acid; or conversely, converting the acid addition salt into the free base with alkali.

25

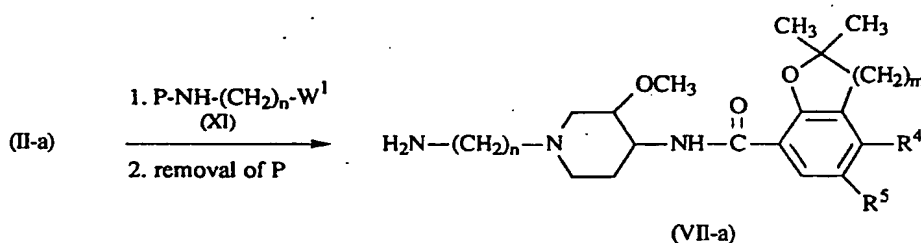
11. A process for preparing a compound of formula (I-a), characterized by

a) preparing an enantiomerically enriched or enantiomerically pure intermediate of formula (XIX-a), wherein A is P¹, said intermediates being represented by (XIV-a),
5 according to claim 9;

b) reacting an enantiomerically enriched or enantiomerically pure intermediate of formula (XIV-a) with an acid of formula (V) or a functional derivative thereof, and subsequently removing the protective group P¹, thus yielding an enantiomerically pure intermediate of
10 formula (II-a);

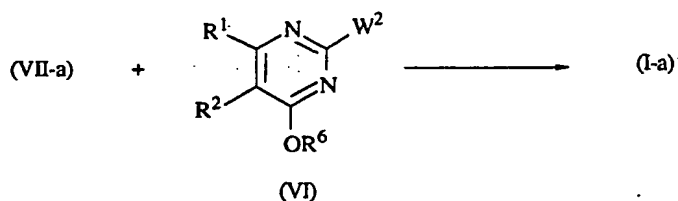


c) N-alkylating an enantiomerically enriched or enantiomerically pure intermediate of formula (II-a) with a reagent of formula (XI), and subsequently removing the protective group P, thus yielding an enantiomerically enriched or enantiomerically pure intermediate of formula (VII-a);
15



20

d) reacting an enantiomerically enriched or enantiomerically pure intermediate of formula (VII-a) with a reagent of formula (VI), wherein R⁶ is hydrogen or C₁₋₆alkyl and W² is an appropriate leaving group and, when necessary, cleaving of the protective ether-function, to yield an enantiomerically enriched or enantiomerically pure compound of
25 formula (I-a);



- and, if desired, further purifying the enantiomerically enriched compounds of formula (I-a) to obtain enantiomerically pure compounds of formula (I-a), and if further desired, converting the compounds of formula (I-a) into a therapeutically active non-toxic acid addition salt form by treatment with acid; or conversely, converting the acid addition salt into the free base with alkali.
- 5.

INTERNATIONAL SEARCH REPORT

PCT/EP 93/03206

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D405/14; A61K31/445; C07D211/42		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 445 862 (JANSSEN PHARMACEUTICA N.V.) 11 September 1991 cited in the application see claim 1	5,6
A	EP,A,0 389 037 (JANSSEN PHARMACEUTICA N.V.) 26 September 1990 cited in the application see claim 1	5,6
A	EP,A,0 309 043 (JANSSEN PHARMACEUTICA N.V.) 29 March 1989 Formula (IV) see claim 11	8,9
--- -/-		
<p>¹⁰ Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
02 FEBRUARY 1994	14. 02. 94	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	GETTINS M.P.	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0 076 530 (JANSSEN PHARMACEUTICA N.V.) 13 April 1983 Formula (II) see claim 11 -----	8,9

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**



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SA 82437

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The members are as contained in the European Patent Office EDP file on
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		CN-A- 1054778	25-09-91
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		US-A- 5185335	09-02-93
		US-A- 5262418	16-11-93
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		US-A- 5137896	11-08-92
		SU-A- 1593569	15-09-90

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

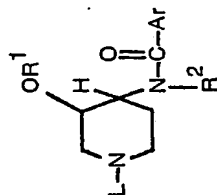
No.	L	R ¹	R ²	Ar	cis/trans isomerism	base/salt form	m.p. °C
58	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	C ₆ H ₆	trans	base	147.0
59	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	4-NH ₂ ,5-CONH ₂ ,2-OCH ₃ -C ₆ H ₂	cis	H ₂ O	127.9—193.9
60	4-F-C ₆ H ₄ -O-(CH ₂) ₅	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	H ₂ O	106.6
61	(C ₆ H ₅) ₂ -N-(CH ₂) ₃	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	H ₂ O	109.1
62	4-F-C ₆ H ₄ -O-(CH ₂) ₆	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	H ₂ O	86.4
63	(4-F-C ₆ H ₄)(4-CH ₃ -C ₆ H ₄ -SO ₂)N-(CH ₂) ₃	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	H ₂ O	109.0
64	(4-F-C ₆ H ₄) ₂ CH-O-(CH ₂) ₂	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	H ₂ O	89.7
65	(C ₆ H ₅) ₂ N-C(O)-(CH ₂) ₂	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	H ₂ O	126.2
66	(4-F-C ₆ H ₄)(4-F-C ₆ H ₄ -C(O))N-(CH ₂) ₃	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	base	183.2
67	(4-F,2-NO ₂ -C ₆ H ₃)-O- 	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	base	—
68	4-F-C ₆ H ₄ -O-CH ₂ CH(CH ₃)CH ₂	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	base	92.3
69	(C ₆ H ₅) ₃ -C-(CH ₂) ₃	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	H ₂ O	148.9
70	[1-(4-F-C ₆ H ₄)-1,3-dihydro-1-isobenzofuranyl] (CH ₂) ₃	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	base	124.3
71	 -O-(CH ₂) ₃	CH ₃	H	4-NH ₂ ,5-Cl,2-OCH ₃ -C ₆ H ₂	cis	base	95.9—100.9

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Example LVIII

A mixture of 4.1 parts of 1-(3-chloropropoxy)-4-fluorobenzene, 4.4 parts of *cis-N*-(3-hydroxy-4-piperidinyl)benzamide, 3.8 parts of sodium carbonate, 0.1 parts of potassium iodide and 160 parts of 4-methyl-2-pentanone was stirred and refluxed for 20 hours. The reaction mixture was cooled to room temperature and washed with water. The organic phase was dried, filtered and evaporated. The residue was crystallized from 2-propanol, yielding 4.2 parts (57%) of *cis-N*-[1-[3-(4-fluorophenoxy)propyl]-3-hydroxy-4-piperidinyl]benzamide; mp. 130.5°C (compound 72).

Following the same procedure and using equivalent amounts of the appropriate starting materials there were also prepared:



No.	L	R ¹	R ²	Ar	cis/trans isomerism	base/salt form	m.p. °C
73	(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-(CH ₂) ₃	H	H	C ₆ H ₅	cis	base	190
74	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	C ₆ H ₅	cis	base	98.2
75	(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-(CH ₂) ₃	CH ₃	H	C ₆ H ₅	cis	base	210.3
76	(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	112.5
77	2-naphthalenyl/methyl	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	156.2
78	(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-(CH ₂) ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	250.5
79	CH ₂ =CH-CH ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	176.3
80	2,6-Cl ₂ -C ₆ H ₃ -NH-CO-CH ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	228.3
81	2,6-Cl ₂ -C ₆ H ₃ -NH-CO-CH ₂ CH ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	206.1

No.	L	R ¹	R ²	Ar	cis/trans isomerism	base/salt form	m.p. °C
82	(5-Cl-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	255.4
83	(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-(CH ₂) ₄	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	1/2 H ₂ O	122.5
84	3-Cl-C ₆ H ₄ -CH=CH-CH ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	H ₂ O	92
85	2,6-(CH ₃) ₂ -C ₆ H ₃ -NHCO(CH ₂) ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	177.1
86	2,6-Cl ₂ -C ₆ H ₃ -CONH-(CH ₂) ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	191.2
87	(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-(CH ₂) ₃	H	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	244.4
88	(1-F-2-CH ₃ CO)C ₆ H ₃ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	H ₂ O	131.4
89	4-F-C ₆ H ₄ -O-CH ₂ -CH ₂ -	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	103.4
90	(2,4-Cl ₂ -C ₆ H ₃)-O-CH(CH ₃)-CH ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	134.2

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Example LIX

5 A mixture of 2.8 parts of 3-(chloromethyl)pyridine hydrochloride, 4.7 parts of *cis*-4-amino-5-chloro-2-methoxy-*N*-(3-methoxy-4-piperidinyl)benzamide, 5.3 parts of sodium carbonate and 68 parts of *N,N*-dimethylformamide was stirred for 5 hours at about 60°C. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated. The solid residue was purified by column-
10 chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from ethanol. The product was filtered off and dried, yielding 3.84 parts (64.2%) of *cis*-4-amino-5-chloro-2-methoxy-*N*-[3-methoxy-1-(3-pyridinylmethyl)-4-piperidinyl]benzamide; mp. 188.9°C (compound 91).
15 Following the same procedure and using equivalent amounts of the appropriate starting materials there were also prepared:

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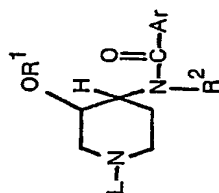
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No.	L	R¹	R²	Ar	cis/trans isomerism	base/salt form	m.p. °C
92	4-F-C ₆ H ₄ -CO-(CH ₂) ₃	CH ₃	H	C ₆ H ₅	cis	base	91.6
93	4-F-C ₆ H ₄ -CO-(CH ₂) ₃	CH ₃	H	C ₆ H ₅	trans	base	178.2
94	4-F-C ₆ H ₄ -CO-(CH ₂) ₃	H	H	C ₆ H ₅	trans	base	149.6
95	4-F-C ₆ H ₄ -CO-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	181.2
96	2-pyridinyl/methyl	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	172.6
97	5-(4-F-C ₆ H ₄)-3-isoxazolyl/methyl	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	146.6
98	4-(1 <i>H</i> -imidazol-1-yl)-phenyl/methyl	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	261.8
99	3-CF ₃ -C ₆ H ₄ -CH ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	138.7
100	(4-F-C ₆ H ₄) ₂ -CH-(CH ₂) ₃	CH ₃	H	C ₆ H ₅	trans	base	97
101	(2-methylimidazo[1,2-a]pyridin-7-yl)methyl	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	H ₂ O	196.5
102	(imidazo[1,2-a]pyridin-7-yl)methyl	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	195.6
103	4-F-C ₆ H ₄ -O-(CH ₂) ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	152.2

No.	L	R ¹	R ²	Ar	cis/trans isomerism	base/salt form	m.p. °C
104	4-F-C ₆ H ₄ -O-(CH ₂) ₄	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	110.3
105	(4-F-C ₆ H ₄) ₂ C(CN)-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	H ₂ O	96.1
106	4-F-C ₆ H ₄ -SO ₂ -(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	179.5
107	2-pyridinylmethyl	C ₂ H ₅	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	173.8
108	2-pyridinylmethyl	H	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	143.3
109	(4-F-C ₆ H ₄) ₂ -C(CON(CH ₃) ₂)-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	H ₂ O	130.6
110	(5-CH ₃ -1 <i>H</i> -imidazol-4-yl)-CH ₂	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	H ₂ O	181.6
111	4-F-2-(4-F-C ₆ H ₄ -CO)-C ₆ H ₅ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	132.5
112	2-NH ₂ CO-4-F-C ₆ H ₃ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	175.3
113	(4-Cl-2-CH ₃ -C ₆ H ₃)-O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	101.6
114	3-CF ₃ -C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	83.2
115	4-NO ₂ -C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	186.8
116	C ₆ H ₅ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	HCl	258.7
117	[2,2-(4-F-C ₆ H ₄) ₂ -1,3-dioxo-lan-4-yl]methyl	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	112.1
118	CH ₃ O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	95.3
119	(C ₆ H ₅) ₂ CH-C(O)-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	157.5
120	(4-F-C ₆ H ₄)(CH ₃ O) ₂ C-CH(OH)-(CH ₂) ₂	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-Cl-C ₆ H ₂	cis	base	215.3
121	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O-4-NH ₂ -5-SOCH ₃ -C ₆ H ₂	cis	H ₂ O	148.6—166.8

Example LX

A mixture of 7.6 parts of *N*-(dihydro-3,3-diphenyl-2(3*H*)-furanylidene)-*N*-methylmethanaminium bromide, 4.7 parts of *cis-N*-(3-methoxy-4-piperidinyl)benzamide, 3.8 parts of sodium carbonate, 0.1 parts of potassium iodide and 240 parts of 4-methyl-2-pentanone was stirred and refluxed for 18 hours using a water-separator. The reaction mixture was cooled to room temperature and washed with water. The organic phase was separated, dried, filtered and evaporated. The oily residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2,2'-oxybispropane. The product was filtered off and dried, yielding 3.5 parts (35%) of *cis*-4-(benzoylamino)-3-methoxy-*N,N*-dimethyl- α,α -diphenyl-1-piperidinebutanamide; m.p. 146.6°C (compound 122).

In a similar manner there were also prepared:

- trans*-4-(benzoylamino)-3-hydroxy-*N,N*-dimethyl- α,α -diphenyl-1-piperidinebutanamide; m.p. 178.4°C (compound 123);
- trans*-4-(benzoylamino)-3-methoxy-*N,N*-dimethyl- α,α -diphenyl-1-piperidinebutanamide (E)-2-butenedioate (1:1); m.p. 163.4°C (compound 124);
- cis*-4-(benzoylamino)-3-hydroxy-*N,N*-dimethyl- α,α -diphenyl-1-piperidinebutanamide ethanedioate (1:1); m.p. 209.9°C (compound 125);
- trans*-4-(benzoylamino)-3-methoxy-*N,N,\gamma*-trimethyl- α,α -diphenyl-1-piperidinebutanamide; m.p. 196.1°C (compound 126);
- trans*-4-(benzoylamino)-3-hydroxy-*N,N,\gamma*-trimethyl- α,α -diphenyl-1-piperidinebutanamide; m.p. 176.7°C (compound 127);
- cis*-4-(benzoylamino)-3-hydroxy-*N,N,\gamma*-trimethyl- α,α -diphenyl-1-piperidinebutanamide; m.p. 198.5°C (compound 128);
- cis*-4-[(4-amino-5-chloro-2-methoxybenzoyl)amino]-3-hydroxy-*N,N,\gamma*-trimethyl- α,α -diphenyl-1-piperidinebutanamide; m.p. 233.4°C (compound 129); and
- cis*-4-[(4-amino-5-chloro-2-methoxybenzoyl)amino]-3-methoxy-*N,N*-dimethyl- α,α -diphenyl-1-piperidinebutanamide monohydrate; m.p. 128.8°C (compound 130).

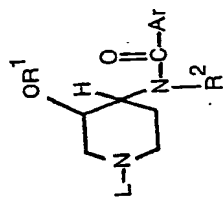
Example LXI

A mixture of 11 parts of 1-(4-fluorobenzoyl)aziridine, 6.28 parts of *cis*-4-amino-5-chloro-2-methoxy-*N*-(3-methoxy-4-piperidinyl)benzamide, 45 parts of benzene and 20 parts of methanol was stirred and refluxed for 6 hours. The reaction mixture was evaporated and the residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile, yielding 5.09 parts of *cis*-4-amino-5-chloro-*N*-[1-[2-[(4-fluorobenzoyl)amino]ethyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide; m.p. 208.7°C (compound 131).

Example LXII

A mixture of 2.73 parts of α -(4-fluorophenyl)oxiraneethanol, 3.3 parts of *cis-N*-(3-hydroxy-4-piperidinyl)-benzamide and 80 parts of ethanol was stirred and refluxed for 4 hours. The reaction mixture was evaporated. The residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The semi-solid residue was crystallized from acetonitrile, yielding 4.5 parts (74.5%) of *cis-N*-[1-[4-(4-fluorophenyl)-2,4-dihydroxybutyl-3-hydroxy-4-piperidinyl]benzamide; m.p. 172.1°C (compound 132).

In a similar manner there were also prepared:



No.	L	R¹	R²	Ar	cis/trans isomerism	base/salt form	m.p. °C
133	4-F-C ₆ H ₄ -CH(OH)CH ₂ CH(OH)CH ₂	H	H	C ₆ H ₅	trans	base	174.1
134	4-F-C ₆ H ₄ -CH(OCH ₃)CH ₂ CH(OH)CH ₂	H	H	C ₆ H ₅	trans	base	167
135	4-F-C ₆ H ₄ -C(OH)(C-C ₃ H ₇)CH ₂ CH(OH)-CH ₂	H	H	C ₆ H ₅	trans	base	166.7
136	4-F-C ₆ H ₄ -C(OH)(C-CH ₃ H ₉)CH ₂ -CH(OH)CH ₂	H	H	C ₆ H ₅	trans	(COOH) ₂	141
137	4-F-C ₆ H ₄ C(OCH ₃) ₂ CH ₂ CH(OH)CH ₂	H	H	C ₆ H ₅	trans	CHCOOH = CHCOOH	199.1
138	(4-F-C ₆ H ₄) ₂ CH-CH ₂ CH(OH)CH ₂	H	H	2-CH ₃ O, 4-NH ₂ , 5-Cl-C ₆ H ₂	cis	base	111.2
139	(4-F-C ₆ H ₄)-O-CH ₂ -CH(OH)-CH ₂	CH ₃	H	2-CH ₃ O, 4-NH ₂ , 5-Cl-	cis	base	79.8
140	C ₆ H ₅ -CH ₂ -N(CH ₃)-CH ₂ -CH(OH)CH ₂	CH ₃	H	2-CH ₃ O, 4-NH ₂ , 5-Cl-	cis	2(COOH) ₂ H ₂ O	146.7
141	(4-F-C ₆ H ₄) ₂ CH-CH ₂ -CH(OH)-CH ₂	CH ₃	H	2-CH ₃ O, 4-NH ₂ , 5-Cl-	cis	1/2H ₂ O	107.6

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Example LXIII

A mixture of 3.8 parts of 3-(2-chloroethyl)-2(1*H*), 4-(3*H*)-quinazolin-2-one, 4.7 parts of *cis*-4-amino-5-chloro-2-methoxy-*N*-(3-methoxy-4-piperidinyl)benzamide, 1.7 parts of sodium hydrogen carbonate, 0.1 parts of potassium iodide and 160 parts of 4-methyl-2-pentanone was stirred and refluxed for 24 hours. Water was added to the reaction mixture. The precipitated product was filtered off and crystallized from *N,N*-dimethylformamide and a small amount of water, yielding 3.3 parts of *cis*-4-amino-5-chloro-*N*-[1-[2-(1,4-dihydro-2,4-dioxo-3-(2*H*)-quinazolinyl)ethyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide; m.p. 270.8°C (compound 142).

In a similar manner there was also prepared:
cis-4-amino-5-chloro-*N*-[1-[4-(4-fluoro-2-hydroxyphenyl)-4-oxobutyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate; m.p. 165.7°C (compound 143).

Example LXIV

4.7 Parts of *cis*-4-amino-5-chloro-2-methoxy-*N*-(3-methoxy-4-piperidinyl)benzamide were dissolved in 160 parts of 2-propanone. Then there were added successively 3.2 parts of [(2-pyrazinyl)methyl] methane-sulfonate (ester) and 1.7 parts of sodium hydrogen carbonate. The whole was stirred and refluxed for 18 hours while nitrogen gas was introduced. The precipitated product was filtered off and the filtrate was evaporated. The residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized twice from acetonitrile, yielding 1.16 parts of *cis*-4-amino-5-chloro-2-methoxy-*N*-[3-methoxy-1-(2-pyrazinylmethyl)-4-piperidinyl]benzamide; m.p. 203.5°C (compound 144).

Example LXV

To a stirred solution of 40 parts of *cis*-*N*-[3-(phenylmethoxy)-4-piperidinyl]benzamide in 153 parts of tetrahydrofuran were added 323 parts of a sodium hydroxide solution 1*N*. Then there was added dropwise a solution of 15.4 parts of ethyl carbonochloridate in 58 parts of tetrahydrofuran at a temperature below 5°C. Upon completion, stirring was continued for 3 hours while cooling in an ice-bath (temp. below 5°C). Dichloromethane was added and the layers were separated. The aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water, dried, filtered and evaporated. The residue was suspended in 2,2'-oxybispropane. The product was filtered off and crystallized from acetonitrile. A first fraction was filtered off, yielding 30.2 parts of *cis*-ethyl 4-(benzoylamino)-3-(phenylmethoxy)-1-piperidinecarboxylate; m.p. 139.2°C. The mother liquor was concentrated. The precipitated product was filtered off, yielding a second fraction of 5 parts of *cis*-ethyl 4-(benzoylamino)-3-(phenylmethoxy)-1-piperidinecarboxylate.

Total yield: 35.2 parts of *cis*-ethyl 4-(benzoylamino)-3-(phenylmethoxy)-1-piperidinecarboxylate (70.8%) (compound 145).

Example LXVI

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol were added 12 parts of an acetaldehyde solution 10% in tetrahydrofuran, 6.3 parts of *cis*-4-amino-5-chloro-2-methoxy-*N*-(3-methoxy-4-piperidinyl)benzamide and 120 parts of methanol. The whole was hydrogenated at normal pressure and at room temperature with 2 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was suspended in a mixture of 2,2'-oxybispropane and petroleum ether. The product was filtered off and crystallized from acetonitrile. The product was filtered off and dried, yielding a first fraction of 2 parts of *cis*-4-amino-5-chloro-*N*-[1-ethyl-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate; m.p. 130.2°C. The mother liquor was concentrated. A second fraction was filtered off, yielding 2.89 parts of *cis*-4-amino-5-chloro-*N*-[1-ethyl-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate; m.p. 150.5°C (compound 146).

In a similar manner there were also prepared:

cis-4-amino-*N*-[1-[4,4-bis(4-fluorophenyl)-1-methylbutyl]-3-methoxy-4-piperidinyl]-5-chloro-2-methoxybenzamide monohydrate; m.p. 121.1°C (compound 147);

cis-4-amino-5-chloro-*N*-[1-(2,3-dihydro-1*H*-inden-2-yl)-3-methoxy-4-piperidinyl]-2-methoxybenzamide; m.p. 237.7°C (compound 148);

cis-4-amino-5-chloro-*N*-[1-[2-(cyclohexyloxy)ethyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide; m.p. 118.5°C (compound 149); and

cis-4-amino-5-chloro-*N*-[1-(2-furanylmethyl)-3-methoxy-4-piperidinyl]-2-methoxybenzamide; m.p. 192.6—195.4°C (compound 150).

Example LXVII

To a stirred solution of 4.3 parts of *trans*-1-[4,4-bis(4-fluorophenyl)butyl]-3-methoxy-4-piperidinamine and 1.27 parts of *N,N*-diethylethanamine in 60 parts of trichloromethane was added dropwise a solution of 2.88 parts of 3,4,5-trimethoxybenzoyl chloride in 45 parts of trichloromethane at a temperature below 5°C. The reaction mixture was allowed to reach slowly room temperature and stirring was continued for 18

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hours at room temperature. The solvent was evaporated. The residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the hydrochloride salt in 2-propanone and 2-propanol. The salt was filtered off and dried, yielding 5.27 parts (75.6%) of *trans-N*-[1-[4,4-bis(4-fluorophenyl)butyl]-3-methoxy-4-piperidinyl]-3,4,5-trimethoxybenzamide monohydrochloride monohydrate; m.p. 135.1°C (compound 151).

Following the same procedure and using equivalent amounts of the appropriate starting materials there were also prepared:

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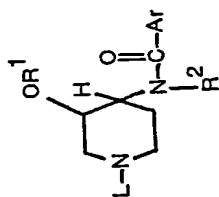
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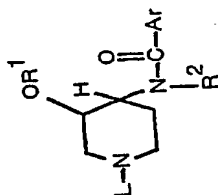
No.	L	R¹	R²	Ar	cis/trans isomerism	base/salt form	m.p. °C
152	C ₂ H ₅ OOCC	H	H	C ₆ H ₅	cis	base	193
153	C ₂ H ₅ OOCC	H	H	C ₆ H ₅	trans	base	158.8
154	C ₂ H ₅ OOCC	CH ₃	H	C ₆ H ₅	cis	base	151.2
155	C ₆ H ₅ -CH ₂	C ₆ H ₅ CH ₂	H	C ₆ H ₅	trans	base	147.4
156	C ₆ H ₅ -CH ₂	CH ₃	H	C ₆ H ₅	trans	base	181.4
157	C ₆ H ₅ -CH ₂	C ₆ H ₅ CH ₂	H	C ₆ H ₅	cis	base	95.5
158	C ₆ H ₅ -CH ₂	CH ₃	H	C ₆ H ₅	cis	base	114.6
159	(4-F-C ₆ H ₄) ₂ CH(CH ₂) ₃	H	CH ₃	4-F-C ₆ H ₄	trans	base	106.5
160	(4-F-C ₆ H ₄) ₂ CH(CH ₂) ₃	H	CH ₃	C ₆ H ₅	trans	base	109.4
161	(4-F-C ₆ H ₄) ₂ CH(CH ₂) ₃	H	H	4-NO ₂ -C ₆ H ₄	trans	base	177
162	(4-F-C ₆ H ₄) ₂ CH(CH ₂) ₃	H	H	C ₆ H ₅	trans	base	175.8
163	(4-F-C ₆ H ₄) ₂ CH(CH ₂) ₃	H	H	3,4,5-(CH ₃ O) ₃ -C ₆ H ₂	trans	base	83.1
164	(4-F-C ₆ H ₄) ₂ CH(CH ₂) ₃	CH ₃	H	4-NO ₂ -C ₆ H ₄	cis	base	118.3
165	(4-F-C ₆ H ₄) ₂ CH(CH ₂) ₃	CH ₃	H	3,4,5-(CH ₃ O) ₃ -C ₆ H ₂	cis	HCl	186.2
166	(4-F-C ₆ H ₄) ₂ CH(CH ₂) ₃	CH ₃	H	C ₆ H ₅	cis	base	124.4
167	(4-F-C ₆ H ₄) ₂ CH(CH ₂) ₃	H	H	3,4,5-(CH ₃ O) ₃ -C ₆ H ₂	cis	HCl.H ₂ O	118.1

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Example LXVIII

To a stirred solution of 22.5 parts of 4-amino-5-chloro-2-methoxybenzoic acid in 405 parts of trichloromethane were added dropwise successively 11.8 parts of *N,N*-diethylethanamine and 13 parts of ethyl carbonochloridate at a temperature below 10°C. Stirring was continued for 45 minutes at a temperature below 10°C. Then there was added dropwise a solution of 19.15 parts of *cis*-ethyl-4-amino-3-methoxy-1-piperidinecarboxylate in 360 parts of trichloromethane at the same temperature. Upon completion, stirring was continued for 18 hours at room temperature. The reaction mixture was washed successively three times with water, once with a 5% sodium hydroxide solution and again twice with water. The organic phase was dried, filtered and evaporated. The residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 29.3 parts (80%) of *cis*-ethyl 4-(amino-5-chloro-2-methoxybenzoylamino)-3-methoxy-1-piperidinecarboxylate as a residue (compound 168).

Following the same procedure and using equivalent amounts of the appropriate starting materials there were also prepared:



No.	L	R¹	R²	Ar	cis/trans isomerism	base/salt form	m.p. °C
169	(4-F-C₆H₄)₂-CH-(CH₂)₃	CH₃	H	2-CH₃O,4-NH₂-C₆H₃	cis	(COOH)₂·H₂O	108.9
170	(4-F-C₆H₄)₂-CH-(CH₂)₃	H	H	2-Cl,4-NO₂-C₆H₃	trans	HCl·H₂O	164.9
171	4-F-C₆H₄-CH₂	CH₃	H	2-CH₃O,4-NH₂,5-CN-C₆H₂	cis	base	227.2
172	(4-F-C₆H₄)₂CH-(CH₂)₃	CH₃	H	2-Cl,4-NO₂-C₆H₃	cis	base	131.1
173	(4-F-C₆H₄)₂CH-(CH₂)₃	CH₃	H	2-CH₃O,4-NH₂,5-Cl-C₆H₂	trans	(COOH)₂	170.8
174	(4-F-C₆H₄)₂CH-(CH₂)₃	H	H	2-CH₃O,4-NH₂-C₆H₃	trans	base	74.5
175	(4-F-C₆H₄)₂CH-(CH₂)₃	H	H	2-CH₃O,5-Cl-C₆H₃	trans	HCl	196.8
176	C₆H₅-CH₂	CH₃	H	2-CH₃O,4-NH(CH₃),5-Cl-C₆H₂	cis	base	201.2
177	C₆H₅-CH₂	H	H	2-CH₃O,4-NH(CH₃),5-Cl-C₆H₂	cis	base	164.5
178	3-CH₃O-C₆H₄-CH₂	CH₃	H	2-CH₃O,4-NH₂,5-Cl-C₆H₂	cis	1/2H₂O	103.1
179	1,3-benzodioxol-5-ylmethyl	CH₃	H	2-CH₃O,4-NH₂,5-Cl-C₆H₂	cis	H₂O	162.1
180	C₆H₅-CH₂	H	H	2-CH₃O,4-NH(CH₃),6-Cl-C₆H₂	trans	base	159.9
181	C₆H₅-CH₂	CH₃	H	2-CH₃O,4-NH(CH₃),6-Cl-C₆H₂	trans	base	125.4

No.	L	R ¹	R ²	Ar	cis/trans isomerism	base/salt form	m.p. °C
182	4-CH ₃ O-C ₆ H ₄ -CH ₂	CH ₃	H	2-OCH ₃ ,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	H ₂ O	119.5
183	(4-F-C ₆ H ₄) ₂ CH-(CH ₂) ₃	H	H	2-OCH ₃ ,4-NH ₂ ,5-Cl-C ₆ H ₂	trans	HCl.H ₂ O	181.5
184	(4-F-C ₆ H ₄) ₂ CH- 	CH ₃	H	2-OCH ₃ ,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	214.1
185	 -CH ₂	CH ₃	H	2-OCH ₃ ,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	177.3
186	(CH ₃) ₂ CH	CH ₃	H	2-OCH ₃ ,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	151.1
187	C ₆ H ₅ CH ₂	H	H	2-OCH ₃ ,5-NH ₂ ,SO ₂ -C ₆ H ₃	cis	base	198.2
188	C ₆ H ₅ CH ₂	H	H	4-CN-C ₆ H ₄	cis	base	154.8
189	C ₆ H ₅ CH ₂	H	H	4-Br-C ₆ H ₄	cis	base	171.7
190	C ₆ H ₅ CH ₂	H	H	2-OC ₂ H ₅ ,4-NH ₂ ,5-NO ₂ -C ₆ H ₂	cis	base	225.4
191	C ₆ H ₅ CH ₂	CH ₃	H	2-OCH ₃ ,4-NH ₂ ,5-Cl-C ₆ H ₂	trans	(COOH) ₂ .H ₂ O	232.1
192	C ₆ H ₅ CH ₂	H	H	2-CH ₃ COO-C ₆ H ₄	cis	base	residue
193	C ₆ H ₅ CH ₂	H	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	trans	base	188.3
194	C ₆ H ₅ CH ₂	H	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	210.1
195	C ₂ H ₅ -OOC	H	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	190.1
196	C ₆ H ₅ CH ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	184.2
197	C ₂ H ₅ -OC(O)	C ₂ H ₅	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	—
198	C ₂ H ₅ -OC(O)	CH ₃	CH ₃	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	—

No.	L	R ¹	R ²	Ar	cis/trans isomerism	base/salt form	m.p. °C
199	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-CN-C ₆ H ₂	cis	H ₂ O	137.7
200	(4,5,6,7-tetrahydro-1H-benzimidazol-2-yl)CH ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	base	221.1
201	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Br-C ₆ H ₂	cis	H ₂ O	105.1
202	C ₆ H ₅ -CH ₂	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-CN-C ₆ H ₂	cis	base	208.3
203	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,4-OH,5-Cl-C ₆ H ₂	cis	H ₂ O	123.2
204	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis(+)	base	129.6
205	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis(-)	base	125.0
206	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,5-C ₃ H ₇ CO-C ₆ H ₃	cis	base	91.4
207	4-F-C ₆ H ₄ -O-(CH ₂) ₃	CH ₃	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	trans	H ₂ O	108.2
208	4-F-C ₆ H ₄ -O-(CH ₂) ₃	(C ₂ H ₅) ₂ (N-(CH ₂) ₂)	H	2-CH ₃ O,4-NH ₂ ,5-Cl-C ₆ H ₂	cis	2HCl.H ₂ O	228.6
209	C ₂ H ₅ -O-CO	CH ₃	H	2-CH ₃ O,4-CH ₃ CO,5-CH ₃ SO-C ₆ H ₂	cis	base	171.4—179.3
210	C ₃ H ₅ -O-CO	CH ₃	H	2-CH ₃ O,4-CH ₃ CONH, 5-CH ₃ S-C ₆ H ₂	cis	base	128.7—137.9

Example LXIX

A mixture of 16.6 parts of *cis*-ethyl 4-(4-amino-5-chloro-2-methoxybenzoylamino)-3-methoxy-1-piperidinecarboxylate, 26.36 parts of potassium hydroxide and 160 parts of 2-propanol was stirred and refluxed for 3 hours. The reaction mixture was evaporated in vacuo on a boiling water-bath. Water was added to the residue and the whole was evaporated again. The residue was boiled in water on a warm water-bath. The precipitated product was filtered off and taken up in trichloromethane. The organic phase was separated, dried, filtered and evaporated. The residue was taken up in methylbenzene. The solid residue was filtered off and dried, yielding 6.7 parts (46%) of *cis*-4-amino-5-chloro-2-methoxy-*N*-(3-methoxy-4-piperidiny)benzamide; m.p. 184.3°C (compound 211).

In a similar manner there were also prepared:

cis-*N*-(3-hydroxy-4-piperidiny)benzamide; m.p. 169.7°C (compound 212);

cis-*N*-(3-methoxy-4-piperidiny)benzamide ethanedioate (1:1); m.p. 219°C (compound 213);

cis-4-amino-5-chloro-*N*-(3-hydroxy-4-piperidiny)-2-methoxybenzamide; m.p. 197.4°C (compound 214);

cis-4-amino-5-chloro-*N*-(3-ethoxy-4-piperidiny)-2-methoxybenzamide monohydrate; m.p. 114.5°C (compound 215);

cis-4-amino-5-chloro-2-methoxy-*N*-(3-methoxy-4-piperidiny)-*N*-methylbenzamide; m.p. 167.4°C (compound 216); and

cis-4-amino-2-methoxy-5-(methylsulfinyl)-*N*-(3-methoxy-4-piperidiny)benzamide as a residue (compound 217).

Example LXX

A solution of 22.9 parts of *trans*-*N*-[3-(phenylmethoxy)-1-(phenylmethyl)-4-piperidiny]benzamide in 200 parts of methanol was hydrogenated at normal pressure and at room temperature with 3 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was suspended in 2,2'-oxybispropane. The product was filtered off and suspended in trichloromethane. The whole was shaken with a dilute ammonium hydroxide solution and the layers were separated. The aqueous phase was evaporated and the solid residue was suspended in 5 parts of water. The product was filtered off and dried, yielding 6 parts of *trans*-*N*-(3-hydroxy-4-piperidiny)benzamide; m.p. 210°C (compound 218).

In a similar manner there were also prepared:

trans-*N*-(3-methoxy-4-piperidiny)benzamide (compound 219); and

cis-4-amino-6-methoxy-*N*'-(3-methoxy-4-piperidiny)-1,3-benzenedicarboxamide hemihydrate; m.p. 194.5°C (compound 220).

Example LXXI

A mixture of 150 parts of *cis*-*N*-[3-(phenylmethoxy)-1-(phenylmethyl)-4-piperidiny]benzamide and 400 parts of methanol was hydrogenated at normal pressure and at room temperature with 9 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding a first fraction of 42 parts of *cis*-*N*-[3-(phenylmethoxy)-4-piperidiny]benzamide.

The mother-liquor was evaporated, yielding 70 parts of *cis*-*N*-[3-(phenylmethoxy)-4-piperidiny]benzamide as an oily residue (compound 221).

Example LXXII

A mixture of 4.14 parts of *trans*-*N*-[1-[4,4-bis(4-fluorophenyl)butyl]-3-hydroxy-4-piperidiny]-4-nitrobenzamide and 120 parts of methanol was hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was converted into the hydrochloride salt in 2-propanol and methylbenzene. The salt was filtered off and crystallized from a mixture of acetonitrile and a small amount of *N,N*-dimethylformamide, yielding 2.59 parts (57.8%) of *trans*-4-amino-*N*-[1-[4,4-bis(4-fluorophenyl)butyl]-3-hydroxy-4-piperidiny]benzamide dihydrochloride; m.p. 240.4°C (compound 222).

In a similar manner there were also prepared:

cis-4-amino-*N*-[1-[4,4-bis(4-fluorophenyl)butyl]-3-methoxy-4-piperidiny]benzamide; m.p. 114.3°C (compound 223);

trans-4-amino-*N*-[1-[4,4-bis(4-fluorophenyl)butyl]-3-hydroxy-4-piperidiny]-2-chlorobenzamide; m.p. 72.4°C (compound 224);

cis-4-amino-*N*-[1-[4,4-bis(4-fluorophenyl)butyl]-3-methoxy-4-piperidiny]-2-chlorobenzamide ethanedioate (1:2) monohydrate; m.p. 100.9°C (compound 225);

cis-4-amino-5-chloro-*N*-[1-[3-(2-amino-4-fluorophenoxy)propyl]-3-methoxy-4-piperidiny]-2-methoxybenzamide; m.p. 183.5°C (compound 226);

cis-4-amino-*N*-[1-[3-(4-aminophenoxy)propyl]-3-methoxy-4-piperidiny]-5-chloro-2-methoxybenzamide; m.p. 170.7°C (compound 227); and

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cis-4-amino-*N*-[1-[4-(2-amino-4-fluorophenoxy)cyclohexyl]-3-methoxy-4-piperidinyl]-5-chloro-2-methoxybenzamide; m.p. 229.7°C (compound 228).

Example LXXIII

5 To a stirred and cooled (ice-bath) solution of 6.64 parts of *cis*-4-amino-5-chloro-*N*-[3-hydroxy-1-(2-pyridinylmethyl)-4-piperidinyl]-2-methoxybenzamide in 68 parts of tetrahydrofuran were added 1.95 parts of *N,N*-diethylethanamine. Then there was added dropwise a solution of 1.41 parts of acetyl chloride in 27 parts of tetrahydrofuran at about 0°C. Upon completion, the mixture was allowed to reach slowly room temperature and stirring was continued for 18 hours at this temperature. Sodium carbonate was added and the whole was evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was washed with water, dried, filtered and evaporated. The residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was further purified by HPLC using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The first fraction was collected and the eluent was evaporated. The residue was suspended in petroleumether. The product was filtered off and dried, yielding 2.03 parts of *cis*-4-[[4-(acetylamino)-5-chloro-2-methoxybenzoyl]amino]-1-(2-pyridinylmethyl)-3-piperidinol acetate (ester); m.p. 179.4°C (compound 229).
15 The second fraction was collected and the eluent was evaporated. The residue was suspended in petroleumether. The product was filtered off and dried, yielding 2.44 parts of *cis*-4-[[4-amino-5-chloro-2-methoxybenzoyl]amino]-1-(2-pyridinylmethyl)-3-piperidinol acetate (ester); m.p. 181.7°C (compound 230).
20

Example LXXIV

To a stirred solution of 7.5 parts of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-hydroxy-4-piperidinyl]-2-methoxybenzamide in 68 parts of tetrahydrofuran were added dropwise 1.94 parts of *N,N*-diethylethanamine. After cooling to 0°C, 1.4 parts of acetyl chloride dissolved in 9 parts of tetrahydrofuran were added dropwise at a temperature below 0°C. Upon completion, stirring was continued for a while in an ice-bath. The mixture was allowed to reach slowly room temperature and stirring was continued overnight at room temperature. The solvent was evaporated and the residue was taken up in a saturate sodium carbonate solution. The product was extracted with methylbenzene. The extract was washed with water, dried, filtered and evaporated. The residue was purified twice by column-chromatography over silica gel using first a mixture of trichloromethane and methanol (95:5 by volume) and then a mixture of trichloromethane, hexane and methanol (48:48:4 by volume) as eluent. The first fraction was collected and the eluent was evaporated. The residue was suspended in petroleumether. The product was filtered off and dried, yielding 0.59 parts of *cis*-4-[[4-(acetylamino)-5-chloro-2-methoxybenzoyl]amino]-1-[3-(4-fluorophenoxy)propyl]-3-piperidinol acetate (ester); m.p. 172.2°C (compound 231).
35

Example LXXV

To a stirred solution of 7.5 parts of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-hydroxy-4-piperidinyl]-2-methoxybenzamide in 68 parts of tetrahydrofuran were added dropwise 2.02 parts of *N,N*-diethylethanamine. After cooling to 0°C, there was added dropwise a solution of 1.4 parts of acetyl chloride in 9 parts of tetrahydrofuran at a temperature below 0°C.
40 Upon completion, stirring was continued for a while while cooling in an ice-bath. The reaction mixture was allowed to reach slowly room temperature and stirring was continued overnight at room temperature. The reaction mixture was evaporated and the residue was taken up in a sodium carbonate solution in water. The product was extracted with methylbenzene. The extract was washed with water, dried, filtered and evaporated. The residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was further separated by HPLC using a mixture of trichloromethane, hexane and methanol (48:48:4 by volume) as eluent. The second fraction (B-isomer) was collected and the eluent was evaporated. The residue was suspended in petroleumether. The product was filtered off and dried, yielding 1.7 parts of *cis*-4-[[4-amino-5-chloro-2-methoxybenzoyl]amino]-1-[3-(4-fluorophenoxy)propyl]-3-piperidinol acetate (ester); m.p. 58.8°C (compound 232).
50

Example LXXVI

55 10 parts of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide were dissolved in 225 parts of hot trichloromethane. After cooling to room temperature, 3.6 parts of *N,N*-diethylethanamine were added. Then there was added dropwise a solution of 1.7 parts of acetyl chloride in 30 parts of trichloromethane: exothermic reaction. The whole was stirred and refluxed for 22 hours. After cooling to room temperature, 0.6 parts of acetyl chloride were added and stirring was continued overnight at reflux. Another 0.6 parts of acetyl chloride were added and stirring was continued overnight at reflux. After cooling again to room temperature, there were added successively 0.6 parts of acetyl chloride and a small amount of *N,N*-dimethyl-4-pyridinamine. Stirring was continued for 22 hours at reflux. The reaction mixture was cooled to room temperature and washed with water. The organic phase was dried, filtered and evaporated. The residue was crystallized twice from acetonitrile, yielding 2.78
65

parts (25.5%) of *cis*-4-(acetylamino)-5-chloro-*N*-[1-[3-(4-fluorophenoxy)-propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide; m.p. 175.6°C (compound 233).

Example LXXVII

5 To 65 parts of a sulfuric acid solution 96% were added portionwise (slowly) 3.6 parts of *cis*-4-amino-5-cyano-*N*-[1-[(4-fluorophenyl)methyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide while cooling in an ice-bath. The reaction mixture was allowed to reach room temperature and stirring was continued for 7 hours at room temperature. The reaction mixture was poured onto crushed ice and the whole was alkalized with ammonium hydroxide. The product was extracted with trichloromethane. The extract was washed
10 with water, dried, filtered and evaporated. The residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The most pure fractions were collected and the eluent was evaporated. The residue was further purified by HPLC using a mixture of methylbenzene and ethanol (90:10 by volume) as eluent. The pure fraction was collected and the eluent was evaporated. The residue was boiled in acetonitrile. The product was filtered off and dried, yielding 2.67
15 parts of *cis*-4-amino-*N*'-[1-[(4-fluorophenyl)methyl]-3-methoxy-4-piperidinyl]-6-methoxy-1,3-benzenedicarboxamide; m.p. 243.7°C (compound 234).

Example LXXVIII

A mixture of 5 parts of *cis*-2-[3-hydroxy-1-(phenylmethyl)-4-piperidinylaminocarbonyl]phenol acetate
20 (ester) and 30 parts of sodium hydroxide solution 1N was stirred and heated for four hours at 60°C. The reaction mixture was cooled to room temperature and neutralized with a hydrochloric acid solution 1N. The product was extracted with 1,1'-oxybisethane. The extract was dried, filtered and evaporated. The residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (85:15 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue
25 solidified on triturating in 2,2'-oxybispropane. The product was filtered off and dried, yielding 1.21 parts (27%) of *cis*-2-hydroxy-*N*-[3-hydroxy-1-(phenylmethyl)-4-piperidinyl]benzamide; m.p. 127.1°C (compound 235).

Example LXXIX

30 285 Parts of sulfuric acid were cooled in an ice-bath and 15.5 parts of *cis*-4-amino-5-cyano-2-methoxy-*N*-[3-methoxy-1-(phenylmethyl)-4-piperidinyl]benzamide were added portionwise while cooling. Upon completion, stirring was continued overnight at room temperature. The reaction mixture was poured onto ice-water and the whole was alkalized with ammonium hydroxide. The product was filtered off and stirred in a mixture of trichloromethane and water. The product was filtered off again and dried, yielding 15.0 parts
35 of *cis*-4-amino-6-methoxy-*N*'-[3-methoxy-1-(phenylmethyl)-4-piperidinyl]-1,3-benzenedicarboxamide (compound 236).

Example LXXX

A mixture of 3.12 parts of *cis*-4-amino-5-chloro-*N*-[1-[4-(4-fluorophenyl)-3-butenyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide and 120 parts of methanol was hydrogenated at normal pressure and at room
40 temperature with 2 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 2.54 parts (81%) of *cis*-4-amino-5-chloro-*N*-[1-[4-(4-fluorophenyl)butyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate; m.p. 132.7°C
45 (compound 237).

Example LXXXI

A mixture of 2.88 parts of *cis*-4-amino-5-chloro-*N*-[1-[4-(4-fluorophenyl)-3-hydroxy-4,4-dimethoxybutyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide, 30 parts of concentrate hydrochloric acid and 25
50 parts of water was stirred for 18 hours at room temperature. 100 Parts of water were added and the whole was alkalized with ammonia. The precipitated product was filtered off and taken up in trichloromethane. The organic phase was separated, dried, filtered and evaporated. The residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) saturated with ammonia, as eluent. The pure fractions were collected and the eluent was evaporated. The
55 residue was taken up in benzene. Upon the addition of petroleum ether, the product was precipitated. It was filtered off and dried, yielding 0.47 parts (16%) of *cis*-4-amino-5-chloro-*N*-[1-[4-(4-fluorophenyl)-3-hydroxy-4-oxobutyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide; m.p. 146.4°C (compound 238).

Example LXXXII

60 40 Parts of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate were boiled in 160 parts of methanol. The product was filtered off while hot and crystallized twice from a mixture of 600 parts of tetrachloromethane and 400 parts of trichloromethane. The product was filtered off, dried and recrystallized from 4-methyl-2-pentanone. The product was filtered off and dried (water-separator) yielding 18.5 parts of *cis*-4-amino-5-chloro-*N*-[2-chloro-4-[[1-[3-
65

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(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-aminocarbonyl]-5-methoxyphenyl]-2-methoxybenzamide; m.p. 181.5°C (compound 239).

Example LXXXIII

To a stirred solution of 4 parts of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide in 64 parts of ethanol was added a solution of 1 part of (Z)-2-butenedioic acid in 16 parts of ethanol and the product was allowed to crystallize. It is filtered off and dried, yielding 4.8 parts (92%) of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide (Z)-2-butenedioate (1:1); m.p. 200.3°C (compound 240).

Following the same procedure there were also prepared:

cis-(+)-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1); m.p. 197.1°C [α] = +6.7327° (c = 1% methanol) (compound 241);

cis-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide sulfate (1:1); m.p. 238.6°C (compound 242);

cis-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1); m.p. 168.1°C (compound 243); and

cis-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrochloride; m.p. 249.7°C (compound 244).

Example LXXXIV

30 Parts of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate were dissolved in 280 parts of methylbenzene at reflux temperature and the solution was stirred and refluxed for 2 hours using a water-separator. 180 Parts of methylbenzene were distilled off. The residue was allowed to cool overnight while stirring. The solid product was filtered off and boiled for 1.50 hours in heptane. The product was filtered off and dried, yielding 23.1 parts of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide; m.p. 131.7—133°C (compound 245).

Example LXXXV

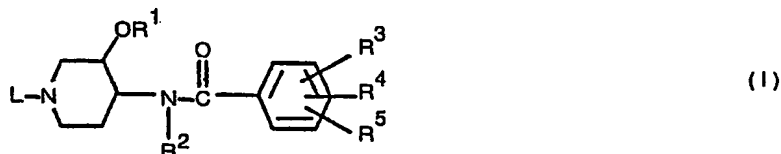
A mixture of 11.6 parts of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide, 3.4 parts of hydrogen peroxide 30%, 270 parts of benzene and 160 parts of methanol was stirred for 5 hours at 60°C. Another 3.4 parts of hydrogen peroxide 30% were added and the whole was stirred overnight at 60°C. The reaction mixture was evaporated to dry. Water was added to the residue and the whole was stirred. The precipitated product was filtered off and crystallized from 2-propanol. The product was filtered off and dried, yielding 5.6 parts of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide, *N*-oxide; m.p. 129.7°C (compound 246).

Example LXXXVI

3.8 Parts of *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide were taken up in 60 parts of acetonitrile. The whole was evaporated and the residue was taken up in methylbenzene. The latter was evaporated again. The residue was dissolved in 60 parts of acetonitrile and 1.16 parts of iodomethane were added. Stirring was continued for 5 hours at room temperature (CaCl₂-tube). The precipitated product was filtered off and boiled in acetonitrile. The product was filtered off while hot, dried and crystallized from methanol. The product was filtered off and recrystallized from water, yielding 0.84 parts of *cis*-4-[(4-amino-5-chloro-2-methoxybenzoyl)amino]-1-[3-(4-fluorophenoxy)propyl]-3-methoxy-1-methylpiperidinium iodide hemihydrate; m.p. 221.5°C (compound 247).

Claims

1. A chemical compound having the formula



the pharmaceutically acceptable acid addition salts, the stereochemically isomeric forms and the pharmaceutically acceptable quaternary ammonium salts thereof, wherein:

R¹ is a member selected from the group consisting of hydrogen, (C₁—C₆) alkyl, (Ar¹)(C₁—C₆) alkyl-carbonyl, amino(C₁—C₆) alkyl and mono- and di[(C₁—C₆) alkyl]amino(C₁—C₆) alkyl;

R² is a member selected from the group consisting of hydrogen and (C₁—C₆) alkyl;

R³, R⁴ and R⁵ are each independently selected from the group consisting of hydrogen, (C₁—C₆) alkyl, (C₁—C₆) alkyloxy, halo, hydroxy, cyano, nitro, amino, mono- and di[(C₁—C₆) alkyl]amino, aminocarbonyl, (Ar¹)carbonylamino, (C₁—C₆) alkylcarbonylamino, (C₁—C₆) alkylcarbonyl, (C₁—C₆) alkylcarbonyloxy, aminosulfonyl, (C₁—C₆) alkylsulfinyl, (C₁—C₆) alkylsulfonyl, (C₁—C₆) alkylthio and mercapto; and

L is a member selected from the group consisting of hydrogen, (C₁—C₆) alkyloxycarbonyl, di(Ar¹)(C₃—C₆) cycloalkyl, (Ar¹O)(C₃—C₆) cycloalkyl, 2,3-dihydro-1*H*-indenyl, a radical having the formula



wherein r is an integer of from 1 to 6 inclusive and R is a member selected from the group consisting of hydrogen, (C₃—C₆) cycloalkyl and Ar²; and a radical having the formula



wherein n is an integer of from 1 to 4 inclusive, X is a member selected from the group consisting of a direct bond, —CH(OH)— and —NH—, m is 0 or an integer of from 1 to 4 inclusive, Y is a member selected from the group consisting of a direct bond, —O—, —CO—, —S—, —SO₂—, —NHCO—, —CONH—, —CH=CH—, —C(OR⁶)(R⁷)—, —CR⁸(Q)— and —NR⁹—, wherein R⁶ is hydrogen or (C₁—C₆) alkyl, R⁷ is hydrogen, (C₃—C₆) cycloalkyl, (C₁—C₆) alkyloxy or (C₁—C₆) alkyl, R⁸ is hydrogen, Ar¹, (C₁—C₆) alkyloxycarbonyl, cyano, aminocarbonyl or mono- or di[(C₁—C₆) alkyl]aminocarbonyl, R⁹ is hydrogen, (C₁—C₆) alkyl, Ar¹, (Ar¹)(C₁—C₆) alkyl, (Ar¹)carbonyl or (Ar¹)sulfonyl and Q is hydrogen, (C₁—C₆) alkyl, (C₃—C₆) cycloalkyl, Ar¹, (Ar¹)(C₁—C₆) alkyl, di(Ar¹)methyl or tri(Ar¹)methyl;

wherein Ar¹ is a member selected from the group consisting of phenyl being optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, hydroxy, (C₁—C₆) alkyl, (C₁—C₆) alkyloxy, aminosulfonyl, (C₁—C₆) alkylcarbonyl, nitro, trifluoromethyl, amino, aminocarbonyl and phenylcarbonyl, said phenyl being optionally substituted with up to 3 halo atoms, and thienyl being optionally substituted with halo or (C₁—C₆) alkyl; and Ar² is a member selected from the group consisting of naphthalenyl, thienyl, pyridinyl, pyrazinyl, 1*H*-indolyl, 1*H*-benzimidazolyl, 2,3-dihydro-2-oxo-1*H*-benzimidazolyl being optionally substituted with 1 or 2 halo atoms, 4,5,6,7-tetrahydro-1*H*-benzimidazolyl, benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, imidazolyl being optionally substituted with a (C₁—C₆) alkyl radical imidazol[1,2-*a*]pyridinyl being optionally substituted with a (C₁—C₆) alkyl radical, 1,4-dihydro-2,4-dioxo-quinazolinyl, isoxazolyl being optionally substituted with an aryl radical, (1*H*-imidazolyl)phenyl, furanyl being optionally substituted with a (C₁—C₆) alkyloxycarbonyl radical, 2,2-di(Ar¹)-1,3-dioxolanyl and 1-(Ar¹)-1,3-dihydro-1-isobenzofuranyl.

2. A chemical compound according to claim 1 wherein R³, R⁴ and R⁵ are, each independently, selected from the group consisting of halo, amino, mono- and di[(C₁—C₆) alkyl]amino and (C₁—C₆) alkyloxy.

3. A chemical compound according to claim 1 wherein R³ is methoxy, R⁴ is amino or methylamino and R⁵ is chloro, said R³, R⁴ and R⁵ being attached to the phenyl ring in the 2-, respectively 4- and 5-positions.

4. A chemical compound selected from the group consisting of 4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide, the pharmaceutically acceptable acid addition salts, the stereochemically isomeric forms and the pharmaceutically acceptable quaternary ammonium salts thereof.

5. A pharmaceutical composition for stimulating the motility of the gastro-intestinal system in vertebrates, comprising an inert carrier material and as an active ingredient a pharmaceutically effective amount of a chemical compound as claimed in any one of claims 1 to 4.

6. A pharmaceutical composition in unit dosage form comprising per dosage unit an effective gastro-intestinal motility stimulating amount of a compound according to claim 1.

7. A pharmaceutical composition according to claim 5 wherein R³ is methoxy, R⁴ is amino or methylamino and R⁵ is chloro, said R³, R⁴ and R⁵ being attached to the phenyl ring in the 2-, respectively 4- and 5-positions.

8. A pharmaceutical composition in unit dosage form comprising per dosage unit an effective gastro-intestinal motility stimulating amount of a compound selected from the group consisting of 4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide, the pharmaceutically acceptable acid addition salts, the stereochemically isomeric forms and the pharmaceutically acceptable quaternary ammonium salts thereof.

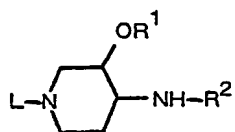
9. A method of preparing a composition as claimed in any one of claims 5 to 8, characterized by mixing an effective amount of a compound as claimed in any one of claims 1 to 4 with an inert carrier.

10. A compound as claimed in any one of claims 1 to 4 or a composition as claimed in any one of claims 5 to 8 for use as a gastro-intestinal stimulant.

11. A process for preparing a chemical compound according to claim 1, characterized by:

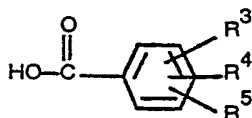
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1) reacting a piperidine of formula



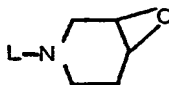
(II)

with a carboxylic acid of formula



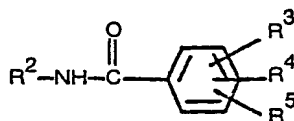
(III)

or an appropriate functional derivative thereof, in a suitable medium; or
2) reacting a 7-oxa-3-azabicyclo[4,1,0]heptane of formula

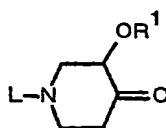


(IV)

with a benzamide of formula

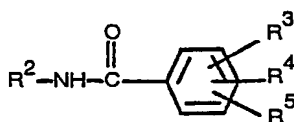


in a suitable medium; or
3) reacting a piperidinone of formula



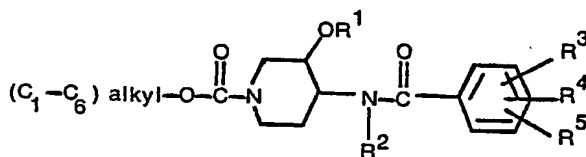
(VII)

with a benzamide of formula



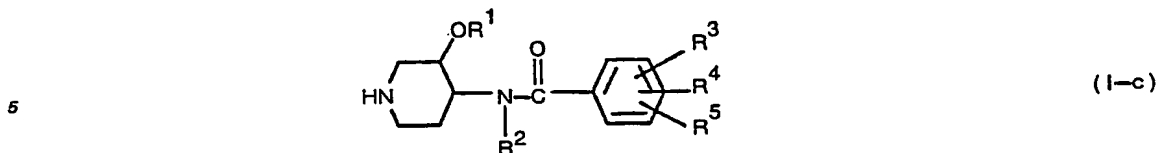
(V)

in a suitable reductive medium; and if desired, where L is a (C₁-C₆) alkyloxycarbonyl radical, converting the compound of formula

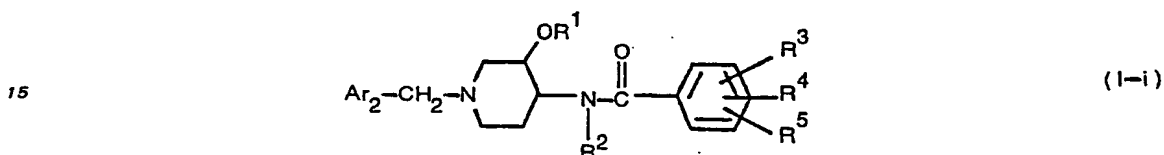


(I-h)

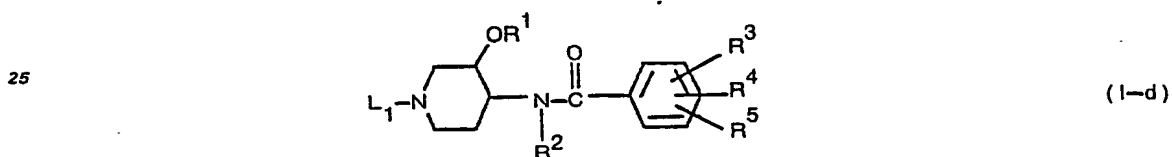
into a compound of formula



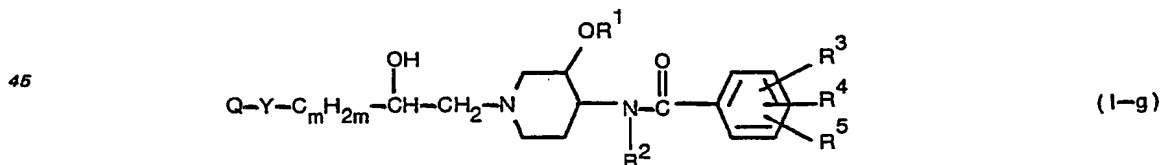
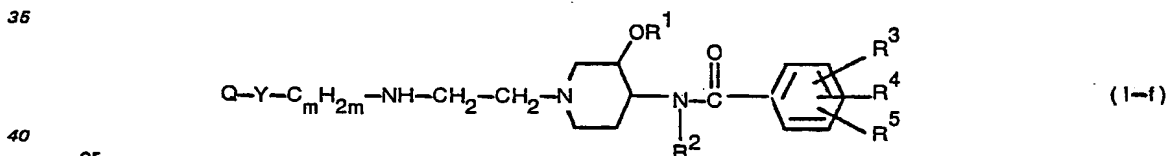
10 by hydrolyzing (I-h) with an appropriate base in a suitable medium; or where L is a $\text{Ar}_2\text{—CH}_2\text{—}$ radical, converting the compound of formula



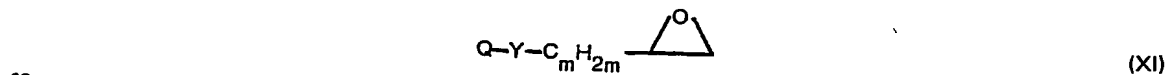
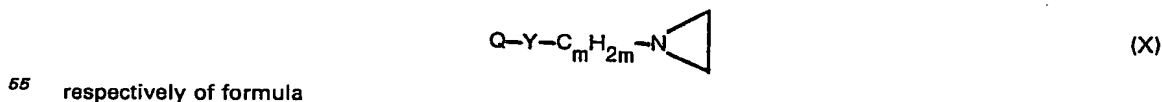
20 into a compound of formula (I-c) by hydrogenolysing (I-i) in a suitable reductive medium; and/or converting a compound of formula (I-c) into a compound of formula



30 wherein L₁ has the meaning of L, provided that hydrogen is excluded, by reacting (I-c) with a reagent of formula $\text{L}_1\text{—W}$ (VIII) or a carbonyl-oxidated form thereof in a suitable medium, respectively a suitable reductive medium; said W being a reactive leaving group; or converting a compound of formula (I-c) into a compound of formula

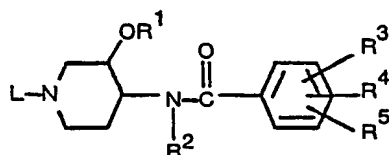


50 by reacting (I-c) with a reagent of formula



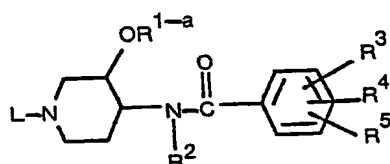
in a suitable medium; and/or where R¹ is hydrogen, converting a compound of formula

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(I-a-1)

into a compound of formula



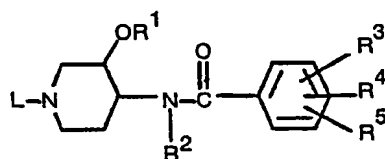
(I-a-2) by reacting (I-a-1)

an appropriate alkylating agent of formula $R^{1-a}-W$ (VI) in a suitable medium, said R^{1-a} having the meaning of R^1 provided that hydrogen is excluded; and, if desired, converting the compounds of formula (I) into the therapeutically active non-toxic acid-addition salt form by treatment with an appropriate acid or, conversely, converting the acid-addition salt into the free base form with alkali; and/or preparing stereochemically isomeric forms thereof; and/or preparing therapeutically active non-toxic quaternary ammonium salts thereof.

12. A process for preparing a chemical compound selected from the group consisting of 4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidiny]-2-methoxybenzamide, the pharmaceutically acceptable acid-addition salts, the stereochemically isomeric forms and the therapeutically active non-toxic quaternary ammonium salts thereof, characterized by reacting 1-(3-chloropropoxy)-4-fluorobenzene with 4-amino-5-chloro-2-methoxy-N-(3-methoxy-4-piperidiny)benzamide in a suitable medium and, if desired, converting the thus obtained 4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidiny]-2-methoxybenzamide into a therapeutically active non-toxic acid-addition salt form by treatment with an appropriate acid; and/or preparing stereochemically isomeric forms thereof; and/or preparing a therapeutically active non-toxic quaternary ammonium salt thereof.

Patentansprüche

1. Eine chemische Verbindung mit der Formel



(I)

die pharmazeutisch annehmbaren Säureadditionssalze, die stereochemisch isomeren Formen und die pharmazeutisch annehmbaren quaternären Ammoniumsalze hiervon, worin:

R^1 ein aus der aus Wasserstoff, $(C_1-C_6)Alkyl$, $(Ar^1)(C_1-C_6)Alkyl$, $(C_1-C_6)Alkylcarbonyl$, Amino $(C_1-C_6)alkyl$ und Mono- und Di $[(C_1-C_6)alkyl]amino$ $(C_1-C_6)alkyl$ bestehenden Gruppe ausgewähltes Glied ist;

R^2 ein aus der aus Wasserstoff und $(C_1-C_6)Alkyl$ bestehenden Gruppe ausgewähltes Glied ist;

R^3 , R^4 und R^5 jeweils unabhängig voneinander aus der aus Wasserstoff, $(C_1-C_6)Alkyl$, $(C_1-C_6)Alkyl$ oxy, Halogen, Hydroxy, Cyano, Nitro, Amino, Mono- und Di $[(C_1-C_6)alkyl]amino$, Aminocarbonyl, $(Ar^1)Carbonylamino$, $(C_1-C_6)Alkylcarbonylamino$, $(C_1-C_6)Alkylcarbonyl$, $(C_1-C_6)Alkylcarbonyloxy$, Aminosulfonyl, $(C_1-C_6)Alkylsulfinyl$, $(C_1-C_6)Alkylsulfonyl$, $(C_1-C_6)Alkylthio$ und Mercapto bestehenden Gruppe ausgewählt sind; und

L ein Glied ist, ausgewählt aus der aus Wasserstoff, $(C_1-C_6)Alkyl$ oxycarbonyl, Di $(Ar^1)(C_3-C_6)cycloalkyl$, $(Ar^1O)(C_3-C_6)Cycloalkyl$, 2,3-Dihydro-1H-indenyl, einem Rest mit der Formel



worin r eine ganze Zahl von 1 bis einschließlich 6 ist und R ein aus der aus Wasserstoff, $(C_3-C_6)Cycloalkyl$ und Ar^2 bestehenden Gruppe ausgewähltes Glied ist; und einem Rest mit der Formel



bestehenden Gruppe, worin n eine ganze Zahl von 1 bis einschließlich 4 ist, X ein aus der aus einer direkten Bindung, $-\text{CH}(\text{OH})-$ und $-\text{NH}-$ bestehenden Gruppe ausgewähltes Glied bedeutet, m Null oder eine ganze Zahl von 1 bis einschließlich 4 bedeutet, Y ein aus der aus einer direkten Bindung, $-\text{O}-$, $-\text{CO}-$, $-\text{S}-$, $-\text{SO}_2-$, $-\text{NHCO}-$, $-\text{CONH}-$, $-\text{CH}=\text{CH}-$, $-\text{C}(\text{OR}^6)(\text{R}^7)-$, $-\text{CR}^8(\text{Q})-$ und $-\text{NR}^9-$ bestehenden Gruppe ausgewähltes Glied ist, worin R^6 Wasserstoff oder $(\text{C}_1-\text{C}_6)\text{Alkyl}$ bedeutet, R^7 Wasserstoff, $(\text{C}_3-\text{C}_6)\text{-Cycloalkyl}$, $(\text{C}_1-\text{C}_6)\text{Alkyloxy}$ oder $(\text{C}_1-\text{C}_6)\text{Alkyl}$ darstellt, R^8 Wasserstoff, Ar^1 , $(\text{C}_1-\text{C}_6)\text{Alkyloxycarbonyl}$, Cyano, Aminocarbonyl oder Mono- oder $\text{Di}[(\text{C}_1-\text{C}_6)\text{alkyl}]$ aminocarbonyl bedeutet, R^9 Wasserstoff, $(\text{C}_1-\text{C}_6)\text{Alkyl}$, Ar^1 , $(\text{Ar}^1)(\text{C}_1-\text{C}_6)\text{Alkyl}$, $(\text{Ar}^1)\text{Carbonyl}$ oder $(\text{Ar}^1)\text{Sulfonyl}$ darstellt und Q Wasserstoff, $(\text{C}_1-\text{C}_6)\text{Alkyl}$, $(\text{C}_3-\text{C}_6)\text{Cycloalkyl}$, Ar^1 , $(\text{Ar}^1)(\text{C}_1-\text{C}_6)\text{Alkyl}$, $\text{Di}(\text{Ar}^1)\text{methyl}$ oder $\text{Tri}(\text{Ar}^1)\text{methyl}$ bedeutet;

10 worin Ar^1 ein Glied bedeutet, ausgewählt aus Phenyl, das gegebenenfalls mit bis zu 3 Substituenten, die jeweils unabhängig voneinander aus der aus Halogen, Hydroxy, $(\text{C}_1-\text{C}_6)\text{Alkyl}$, $(\text{C}_1-\text{C}_6)\text{Alkyloxy}$, Aminosulfonyl, $(\text{C}_1-\text{C}_6)\text{Alkylcarbonyl}$, Nitro, Trifluormethyl, Amino, Aminocarbonyl und Phenylcarbonyl bestehenden Gruppe ausgewählt sind, welches Phenyl gegebenenfalls mit bis zu drei Halogenatomen substituiert ist, und aus gegebenenfalls mit Halogen oder $\text{C}_1-\text{C}_6\text{-Alkyl}$ substituiertem Thienyl; und Ar^2 ein
15 Glied ist, ausgewählt aus der aus Naphthalenyl, Thienyl, Pyridinyl, Pyrazinyl, 1*H*-Indolyl, 1*H*-Benzimidazolyl, 2,3-Dihydro-2-oxo-1*H*-benzimidazolyl, das gegebenenfalls mit einem oder mit zwei Halogenatomen substituiert ist, 4,5,6,7-Tetrahydro-1*H*-benzimidazolyl, Benzodioxolyl, 2,3-Dihydro-1,4-benzodioxinyl, Imidazolyl, das gegebenenfalls mit einem $\text{C}_1-\text{C}_6\text{-Alkylrest}$ substituiert ist, Imidazo[1,2-*a*]pyridinyl, das
20 gegebenenfalls mit einem $\text{C}_1-\text{C}_6\text{-Alkylrest}$ substituiert ist, 1,4-Dihydro-2,4-dioxochinazolinyl, Isoxazolyl, das gegebenenfalls mit einem Arylrest substituiert ist, (1*H*-Imidazolyl)phenyl, Furanyl, das gegebenenfalls mit einem $(\text{C}_1-\text{C}_6)\text{Alkyloxycarbonylrest}$ substituiert ist, 2,2-Di(Ar^1)-1,3-dioxolanyl und 1-(Ar^1)-1,3-Dihydro-1-isobenzofuranyl bestehenden Gruppe.

2. Eine chemische Verbindung nach Anspruch 1, worin R^3 , R^4 und R^5 jeweils unabhängig voneinander aus der aus Halogen, Amino, Mono- und $\text{Di}[(\text{C}_1-\text{C}_6)\text{alkyl}]$ amino und $(\text{C}_1-\text{C}_6)\text{Alkyloxy}$ bestehenden Gruppe
25 ausgewählt sind.

3. Eine chemische Verbindung nach Anspruch 1, worin R^3 Methoxy bedeutet, R^4 Amino oder Methylamino darstellt und R^5 Chlor ist, wobei die genannten Reste R^3 , R^4 und R^5 in der 2-, 4- bzw. 5-Stellung an den Phenylring gebunden sind.

4. Eine chemische Verbindung, ausgewählt aus der aus 4-Amino-5-chlor-*N*-[1-[3-(4-fluorphenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamid, den pharmazeutisch annehmbaren Säureadditionssalzen, den stereochemisch isomeren Formen und den pharmazeutisch annehmbaren quaternären Ammoniumsalzen hievon bestehenden Gruppe.
30

5. Eine pharmazeutische Zusammensetzung zur Stimulierung der Motilität des Gastro-Intestinalsystems in Vertebraten, umfassend ein inertes Trägermaterial und als eine wirksame Komponente eine pharmazeutisch wirksame Menge einer chemischen Verbindung, wie in einem der Ansprüche 1 bis 4 beansprucht.
35

6. Eine pharmazeutische Zusammensetzung in Dosiseinheitsform, umfassend je Dosiseinheit eine wirksame, die Gastro-Intestinalmotilität stimulierende Menge einer Verbindung gemäß Anspruch 1.

7. Eine pharmazeutische Zusammensetzung nach Anspruch 5, worin R^3 Methoxy bedeutet, R^4 Amino oder Methylamino darstellt und R^5 Chlor ist, wobei die genannten Reste R^3 , R^4 und R^5 in der 2-, 4- bzw. 5-Stellung an den Phenylring gebunden sind.
40

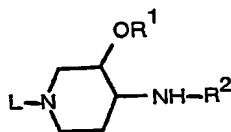
8. Eine pharmazeutische Zusammensetzung in Dosiseinheitsform, umfassend je Dosiseinheit eine wirksame, die Gastro-Intestinal-Motilität stimulierende Menge einer Verbindung, ausgewählt aus der 4-Amino-5-chlor-*N*-[1-[3-(4-fluorphenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamid, die pharmazeutisch annehmbaren Säureadditionssalze, die stereochemisch isomeren Formen und die pharmazeutisch annehmbaren quaternären Ammoniumsalze hievon bestehenden Gruppe.
45

9. Ein Verfahren zur Herstellung einer Zusammensetzung, wie in einem der Ansprüche 5 bis 8 beansprucht, gekennzeichnet durch Vermischen einer wirksamen Menge einer Verbindung, wie in einem der Ansprüche 1 bis 4 beansprucht, mit einem inerten Träger.
50

10. Eine Verbindung, wie in einem der Ansprüche 1 bis 4 beansprucht, oder eine Zusammensetzung, wie in einem der Ansprüche 5 bis 8 beansprucht, zur Verwendung als ein Gastro-Intestinal-Stimulator.

11. Ein Verfahren zur Herstellung einer chemischen Verbindung gemäß Anspruch 1, gekennzeichnet durch:

1) Umsetzen eines Piperidins der Formel
55



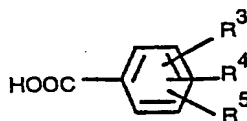
(II)

mit einer Carbonsäure der Formel
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(III),

oder einem geeigneten funktionellen Derivat hiervon in einem geeigneten Medium; oder
2) Umsetzen eines 7-Oxa-3-azabicyclo[4,1,0]heptans der Formel

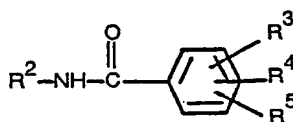
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(IV)

15 mit einem Benzamid der Formel

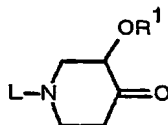
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(V)

in einem geeigneten Medium; oder
3) Umsetzen eines Piperidons der Formel

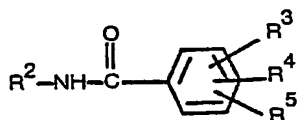
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(VII)

mit einem Benzamid der Formel

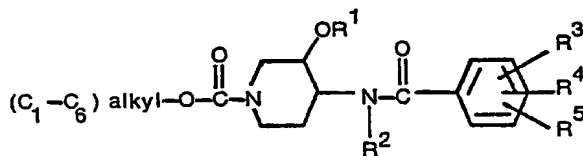
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(V)

in einem geeigneten reduzierenden Medium; und, falls gewünscht, wenn L einen (C₁-C₆)Alkyloxy-carbonylrest bedeutet, Überführen der Verbindung der Formel

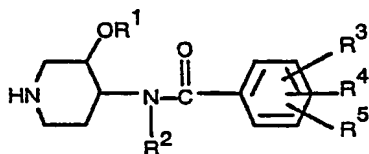
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(I-h)

in eine Verbindung der Formel

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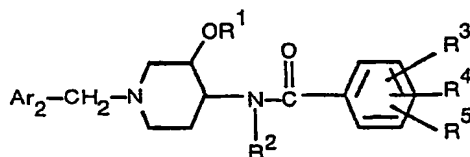


(I-c)

durch Hydrolysieren (I-h) mit einer geeigneten Base in einem geeigneten Medium; oder, wenn L einen Ar₂-CH₂-Rest bedeutet, Überführen der Verbindung der Formel

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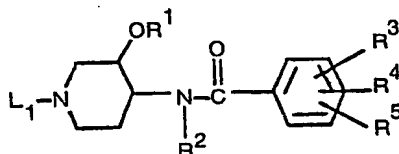
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(I-i)

10 in eine Verbindung der Formel (I-c) durch Hydrogenolysieren von (I-i) in einem geeigneten reduzierenden Medium; und/oder Überführen einer Verbindung der Formel (I-c) in eine Verbindung der Formel

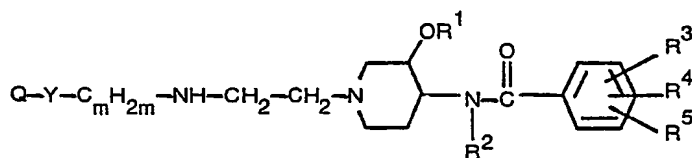
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(I-d)

20 worin L₁ die Bedeutung von L mit der Ausnahme von Wasserstoff aufweist, durch Umsetzen von (I-c) mit einem Reaktionsmittel der Formel L₁-W (VIII) oder einer Carbonyl-oxidierten Form hiervon in einem geeigneten Medium bzw. in einem geeigneten reduzierenden Medium; wobei der genannte Rest W eine reaktionsfähige Leaving-Gruppe bedeutet; oder Überführen einer Verbindung der Formel (I-c) in eine Verbindung der Formel

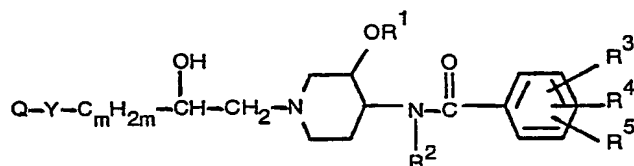
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(I-f)

oder

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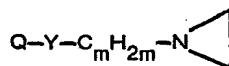


(I-g)

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durch Umsetzen von (I-c) mit einem Reaktionsmittel der Formel

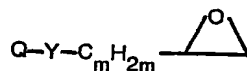
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(X)

bzw. der Formel

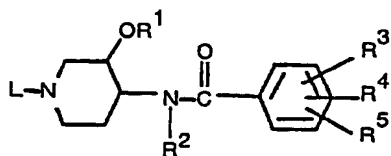
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(XI)

in einem geeigneten Medium; und/oder, falls R¹ Wasserstoff bedeutet, Überführen einer Verbindung der Formel

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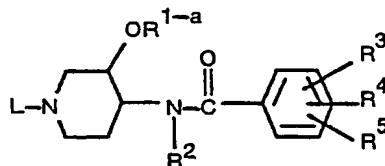


(I-a-1)

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in eine Verbindung der Formel

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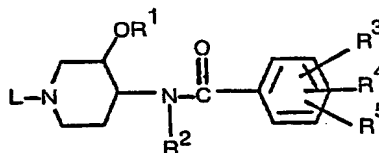
(I-a-2)

durch Umsetzen von (I-a-1) mit einem geeigneten Alkylierungsmittel der Formel $R^{1-a}-W$ (VI) in einem geeigneten Medium, wobei der genannte Rest R^{1-a} die für R^1 angegebene Bedeutung, ausgenommen Wasserstoff, aufweist; und, falls erwünscht, Überführen der Verbindungen der Formel (I) in die therapeutisch wirksame nichttoxische Säureadditionssalzform durch Behandlung mit einer entsprechenden Säure oder umgekehrt Überführen des Säureadditionssalzes mit Alkali in die freie Basenform; und/oder Bereiten stereochemisch isomerer Formen hiervon; und/oder Bereiten therapeutisch wirksamer, nicht-toxischer, quaternärer Ammoniumsalze hiervon.

12. Ein Verfahren zur Herstellung einer chemischen Verbindung ausgewählt aus der aus 4-Amino-5-chlor-*N*-[1-[3-(4-fluorphenoxy)propyl]-3-methoxy-4-piperidiny]-2-methoxybenzamid, den pharmazeutisch annehmbaren Säureadditionssalzen, den stereochemisch isomeren Formen und den therapeutisch wirksamen, nichttoxischen, quaternären Ammoniumsalzen hiervon bestehenden Gruppe, gekennzeichnet durch Umsetzen von 1-(3-Chlorpropoxy)-4-fluorbenzol mit 4-Amino-5-chlor-2-methoxy-*N*-(3-methoxy-4-piperidiny)benzamid in einem geeigneten Medium und gewünschtenfalls Überführen des solcherart erhaltenen 4-Amino-5-chlor-*N*-[1-[3-(4-fluorphenoxy)propyl]-3-methoxy-4-piperidiny]-2-methoxybenzamids in eine therapeutisch wirksame nichttoxische Säureadditionssalzform durch Behandeln mit einer entsprechenden Säure; und/oder Bereiten stereochemisch isomerer Formen hiervon; und/oder Bereiten eines therapeutisch wirksamen, nichttoxischen, quaternären Ammoniumsalzes hiervon.

Revendications

1. Un composé chimique répondant à la formule



(I)

leurs sels d'addition d'acides convenant en pharmacie, leurs formes isomères stéréochimiques et leurs sels d'ammonium quaternaire convenant en pharmacie, dans laquelle:

R^1 est choisi dans le groupe constitué par l'hydrogène, un alkyle (C_1-C_6), un (Ar^1)alkyle(C_1-C_6), un alkyl(C_1-C_6)carbonyle, un amino-alkyle(C_1-C_6) et un mono- et di[(alkyl)(C_1-C_6)]amino-alkyle(C_1-C_6);

R^2 est choisi dans le groupe constitué par un hydrogène et un alkyle(C_1-C_6);

R^3 , R^4 et R^5 sont chacun indépendamment choisis parmi un hydrogène, un alkyle(C_1-C_6), un alcoxy(C_1-C_6), un halogéno, un hydroxy, un cyano, un nitro, un amino, un mono- et di[(alkyl)(C_1-C_6)]amino, un aminocarbonyle, un (Ar^1)carbonylamino, un alkyl(C_1-C_6)carbonylamino, un alkyl(C_1-C_6)carbonyle, un alkyl(C_1-C_6)carbonyloxy, un aminosulfonyle, un alkyl(C_1-C_6)sulfinyle, un alkyl(C_1-C_6)sulfonyle, un alkylthio(C_1-C_6) et un mercapto; et

L est choisi dans le groupe constitué par un hydrogène, un alcoxy(C_1-C_6)carbonyle, un di(Ar^1)cycloalkyle(C_3-C_6), un (Ar^1O)cycloalkyle(C_3-C_6), un 2,3-dihydro-1H-indényle, un radical de formule



dans laquelle r est un entier de 1 à 6 inclusivement et R est choisi parmi un hydrogène, un cycloalkyle (C_3-C_6) et Ar^2 ; et un radical de formule



dans laquelle n est un entier de 1 à 4 inclusivement, X est choisi parmi une simple liaison, $-CH(OH)-$ et $-NH-$, m est 0 ou un entier de 1 à 4 inclusivement, Y est choisi dans le groupe constitué par une simple liaison, $-O-$, $-CO-$, $-S-$, $-SO_2-$, $-NHCO-$, $-CONH-$, $-CH=CH-$, $-C(OR^6)(R^7)-$, $-CR^8(Q)-$ et $-NR^9-$, où R^6 est un hydrogène ou un alkyle(C_1-C_6), R^7 est un hydrogène, un cycloalkyle (C_3-C_6), un alcoxy(C_1-C_6) ou un alkyle(C_1-C_6), R^8 est un hydrogène, Ar^1 , un alcoxy(C_1-C_6)carbonyle, un cyano, un

aminocarbonyle ou un mono- ou di(alkyl(C₁—C₆))aminocarbonyle, R⁹ est un hydrogène, un alkyle(C₁—C₆), Ar¹, un (Ar¹)alkyle(C₁—C₆), un (Ar¹)carbonyle ou un (Ar¹)sulfonyle et Q est un hydrogène, un alkyle(C₁—C₆), un cycloalkyle(C₃—C₆), Ar¹, un (Ar¹-alkyle(C₁—C₆)), un di(Ar¹)méthyle ou un tri(Ar¹)méthyle;

où Ar¹ est choisi dans le groupe constitué par un phényle, éventuellement substitué par jusqu'à trois substituants choisis chacun indépendamment parmi un halogéno, un hydroxy, un alkyle(C₁—C₆), un alcoxy(C₁—C₆), un aminosulfonyle, un alkyl(C₁—C₆)carbonyle, un nitro, un trifluorométhyle, un amino, un aminocarbonyle et un phénylcarbonyle, ledit phényle étant éventuellement substitué avec jusqu'à 3 atomes d'halogène, et un thiényle éventuellement substitué avec un halogéno ou un alkyle(C₁—C₆); et Ar² est choisi parmi un naphthyle, un thiényle, un pyridyle, un pyrazinyle, un 1H-indolye, un 1H-benzimidazole, un 2,3-dihydro-2-oxo-1H-benzimidazole éventuellement substitué avec 1 ou 2 atomes d'halogène, un 4,5,6,7-tétrahydro-1H-benzimidazole, un benzodioxolye, un 2,3-dihydro-1,4-benzodioxynyle, un imidazolyle éventuellement substitué par un radical alkyle(C₁—C₆), un imidazo[1,2-a]pyridyle éventuellement substitué par un radical alkyle(C₁—C₆), un 1,4-dihydro-2,4-dioxoquinazolinyle, un isoxazolyle éventuellement substitué par un radical aryle, un (1H-imidazolyl)phényle, un furyle éventuellement substitué par un radical alcoxy(C₁—C₆)carbonyle, un 2,2-di(Ar¹)-1,3-dioxolannyle et un 1-(Ar¹)-1,3-dihydro-1-isobenzofuryle.

2. Un composé chimique selon la revendication 1 où R³, R⁴ et R⁵ sont chacun indépendamment choisis dans le groupe constitué par un halogéno, un amino, un mono- et un di[(alkyl(C₁—C₆))amino et un alcoxy-(C₁—C₆).

3. Un composé chimique selon la revendication 1 où R³ est un méthoxy, R⁴ est un amino ou un méthylamino et R⁵ est un chloro, lesdits R³, R⁴ et R⁵ étant respectivement fixés au cycle phényle dans les positions 2, 4 et 5.

4. Un composé chimique choisi dans le groupe constitué par le 4-amino-5-chloro-N-[1-[3-(4-fluorophénoxy)propyl]-3-méthoxy-4-pipéridyl]-2-méthoxybenzamide, ses sels d'addition d'acides convenant en pharmacie, ses formes isomères stéréochimiques et ses sels d'ammonium quaternaire convenant en pharmacie.

5. Une composition pharmaceutique pour stimuler la motilité du système gastro-intestinal chez les vertébrés comprenant une matière support inerte et comme ingrédients actifs une quantité pharmaceutique efficace d'un composé chimique comme revendiqué dans l'une quelconque des revendications 1 à 4.

6. Une composition pharmaceutique sous forme d'une dose unitaire d'administration comprenant par dose unitaire une quantité efficace stimulant la motilité gastro-intestinale d'un composé selon la revendication 1.

7. Une composition pharmaceutique selon la revendication 5 dans laquelle R³ est un méthoxy, R⁴ est un amino ou un méthylamino et R⁵ est un chloro, lesdits R³, R⁴ et R⁵ étant fixés respectivement au cycle phényle dans les positions 2, 4 et 5.

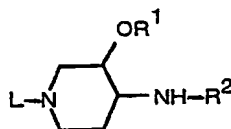
8. Une composition pharmaceutique sous forme d'une dose unitaire d'administration comprenant par dose unitaire une quantité efficace stimulant la motilité gastro-intestinale d'un composé choisis dans le groupe du 4-amino-5-chloro-N-[1-[3-(4-fluorophénoxy)propyl]-3-méthoxy-4-pipéridyl]-2-méthoxybenzamide, ses sels d'addition d'acides convenant en pharmacie, ses formes isomères stéréochimiques et ses sels d'ammonium quaternaire convenant en pharmacie.

9. Un procédé de préparation d'une composition comme revendiqué dans l'une quelconque des revendications 5 à 8 caractérisé par le mélange d'une quantité efficace d'un composé comme revendiqué dans l'une quelconque des revendications 1 à 4 avec un support inerte.

10. Un composé comme revendiqué dans l'une quelconque des revendications 1 à 4 ou une composition comme revendiqué dans l'une quelconque des revendications 5 à 8 pour l'emploi comme stimulant gastro-intestinal.

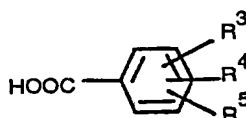
11. Un procédé de préparation d'un composé chimique selon la revendication 1 caractérisé par:

1) la réaction d'une pipéridine de formule



(II)

avec un acide carboxylique de formule

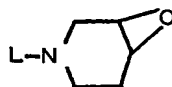


(III),

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ou un dérivé fonctionnel approprié de celui-ci, dans un milieu approprié; ou
2) la réaction d'un 7-oxa-3-azabicyclo[4.1.0]heptane de formule

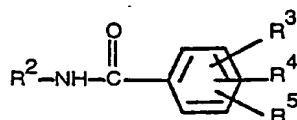
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(IV)

avec un benzamide de formule

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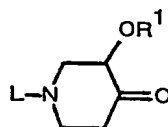


(V)

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dans un milieu approprié; ou
3) la réaction d'une pipéridinone de formule

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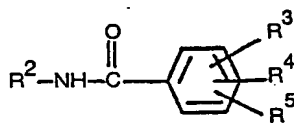


(VII)

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avec un benzamide de formule

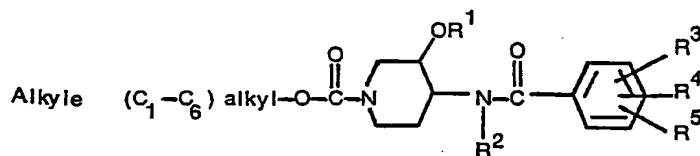
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(V)

35 dans un milieu réducteur approprié et au besoin, lorsque L est un radical alcoxy(C₁-C₆)carbonyle, la conversion du composé de formule

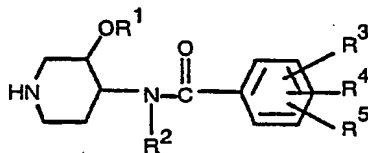
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(I-h)

45 en un composé de formule

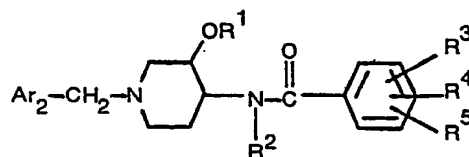
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(I-c)

55 par hydrolyse de (I-h) avec une base appropriée dans un milieu approprié; ou, lorsque L est un radical Ar₂-CH₂-, la conversion du composé de formule

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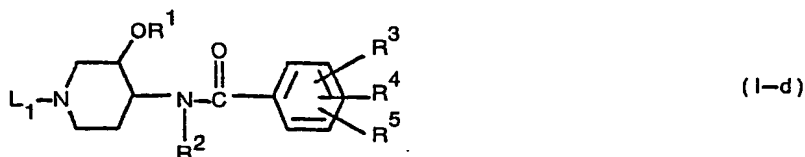


(I-i)

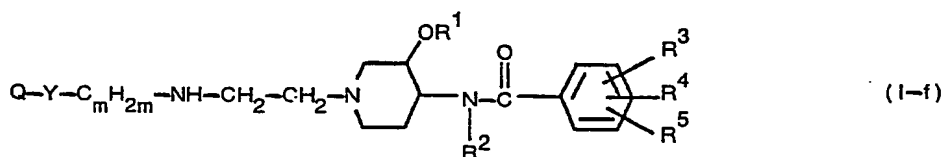
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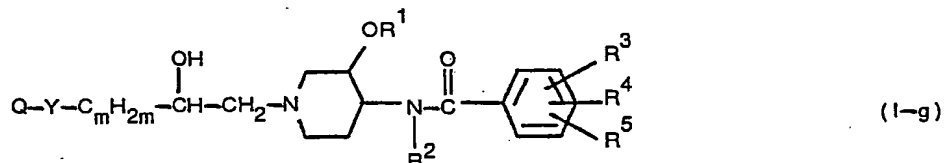
en un composé de formule (I-c) par hydrogénolyse de (I-i) dans un milieu réducteur approprié; et/ou la conversion d'un composé de formule (I-c) en un composé de formule



dans laquelle L₁ a la signification de L, à l'exclusion de l'hydrogène, par réaction de (I-c) avec un composé réagissant de formule L₁-W (VIII) ou une forme carbonyle-oxydée de celui-ci dans un milieu approprié, respectivement un milieu réducteur approprié; ledit W étant un groupe réactif labile; ou la conversion d'un composé de formule (I-c) en un composé de formule



ou



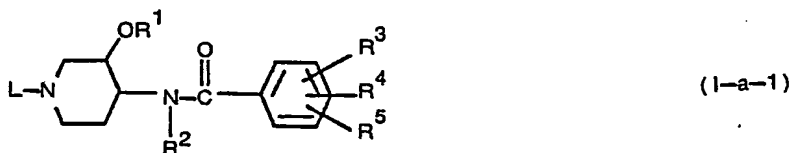
par réaction de (I-c) respectivement avec un composé réagissant de formule



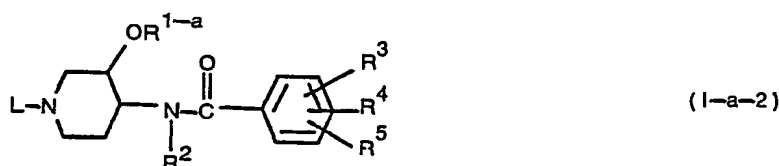
ou de formule



dans un milieu approprié; et/ou lorsque R¹ est un hydrogène, la conversion d'un composé de formule



en un composé de formule



par réaction de (I-a-1) avec un agent d'alkylation approprié de formule R¹-a-W (VI) dans un milieu approprié, ledit R¹-a ayant la signification de R¹ à l'exclusion de l'hydrogène; et, au besoin, la conversion

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des composés de formule (I) en un sel d'addition d'acide non toxique actif en thérapeutique par traitement avec un acide approprié ou inversement la conversion du sel d'addition d'acide en la base libre avec un alcali; et/ou la préparation de leurs formes isomères stéréochimiques; et/ou la préparation de leurs sels d'ammonium quaternaire non toxiques à activité thérapeutique.

- 5 12. Un procédé pour la préparation d'un composé chimique choisi dans le groupe du 4-amino-5-chloro-N-[1-(3-(4-fluorophénoxy)propyl)-3-méthoxy-4-pipéridyl]-2-méthoxybenzamide, ses sels d'addition d'acides convenant en pharmacie, ses formes isomères stéréochimiques et ses sels d'ammonium quaternaire non toxiques à activité thérapeutique, caractérisé par la réaction du 1-(3-chloropropoxy)-4-fluorobenzène avec le 4-amino-5-chloro-2-méthoxy-N-(3-méthoxy-4-pipéridyl) benzamide dans un milieu
10 approprié et au besoin la conversion du 4-amino-5-chloro-N-[1-(3-(4-fluorophénoxy)propyl)-3-méthoxy-4-pipéridyl]-2-méthoxybenzamide en un sel d'addition d'acide non toxique à activité thérapeutique par traitement avec un acide approprié; et/ou la préparation de ses formes isomères stéréochimiques; et/ou la préparation d'un de ses sels d'ammonium quaternaire non toxiques à activité thérapeutique.

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